

**HIGH BLOOD
PRESSURE**

HIGH BLOOD PRESSURE

By

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PREFACE

FIFTEEN years ago, my late chief, Sir Thomas Lewis, asked me to write a book on high blood pressure, pointing out the need for a critical review of the subject. At that time I felt that, while I could be critical, I could not be constructive, because I lacked a theme. Since then, however, chance encounter with new facts has stimulated new ideas which provide a theme around which many of the known facts concerning high blood pressure seem to fall into place.

The central purpose of this book is thus to explain these views on the pathogenesis and course of essential hypertension and to relate them to established knowledge. New ideas come when a newly discovered fact throws unexpected light on an old problem. I have therefore thought it right to treat the problem of high blood pressure broadly, reviewing all those aspects which the reader might expect to find in works on physiology, pathology and medicine. The advancement of knowledge resembles the siege of a fortress in that a constant search is made for a weak place in the defences through which a decisive attack may be launched. In thus attempting to encircle the objective, it is my hope that the reader may see an opportunity for attack that has been hitherto overlooked.

The book is addressed to all those who are interested in the problem of high blood pressure, whether they are students, scientists or practitioners of medicine. To do so is, in a sense, to declare an article of faith, namely that the antithesis sometimes made between the science and practice of medicine is false and mischievous. Good practice depends on exact knowledge, and exact knowledge is most quickly and certainly won by the scientific method. Conversely, good science depends on familiarity with the material investigated. Although work on animals may point the way, the decisive evidence concerning human disease must always come from a study of the patients themselves.

G. W. PICKERING.

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My deepest debt is to those who have worked in this field, and particularly to those with whom I have myself worked. Most of these receive acknowledgment through references in text, tables and figures. But I am well aware that many who should have been included have been omitted, and I have not always succeeded in giving credit for priority when it was due. To them I offer my apologies. Authors and publishers have been generous in making available published figures and tables which are acknowledged as they occur. I am also indebted to Drs N. Ashton, E. T. Bell, F. Byrom, R. H. Heptinstall, E. Neumark, R. Porter, H. Spencer and Professor C. Wilson for original micrographs. For advice and assistance with illustrations I am indebted to Dr. Cardew and his staff. Finally, I find it hard adequately to express my gratitude to Dr. Poul Bechgaard and his colleagues, Drs. Kopp and Nielsen, and to Drs. Cleland, Counihan and Goodwin for allowing me to quote and illustrate so extensively from their most important contributions before publication.

CHAPTER 1

INTRODUCTION

THE IMPORTANCE OF HIGH BLOOD PRESSURE

WITHIN the last 100 years, the implications of Pasteur's germ theory of disease, together with improvements in the social conscience and standards of living, have greatly increased expectation of life, particularly through reduced mortality from infectious diseases. In England and Wales the expectation of life for a child at birth rose from forty and forty-two years for males and females, respectively, in 1841, to forty-eight and fifty-two years in 1901, and to sixty-six and seventy-one years in 1951. Similar figures might be quoted for most of Western Europe and North America, and less strikingly elsewhere. The chief causes of death in Western Europe and North America are now cardiovascular disease and cancer. Thus, in England and Wales there were nearly half a million deaths in 1952. Of these about 18 per cent. were due to cancer, 14 per cent. to vascular lesions affecting the central nervous system, 12 per cent. to coronary and arteriosclerotic heart disease, 15 per cent. to "chronic endocarditis and other myocardial degeneration," and 4 per cent. to hypertension with or without heart disease. These figures must not be examined too closely since the errors involved in certification of death are well known. But they do suggest that vascular disease is now the commonest cause of death in this country. Though both cancer and cardiovascular diseases are predominantly affections of an ageing population, and for that reason may be regarded as of less biological importance, they not infrequently terminate life at what civilized society would regard as its most productive period. These two groups of diseases are, therefore, often regarded as the two greatest contemporary challenges to medical science.

The investigation of the degenerative vascular diseases affecting ageing subjects is hindered by the fact that it is usually difficult, and sometimes impossible, to detect the presence of these lesions until a major vascular disaster has occurred, while the full extent and nature of the vascular change is often only revealed *post mortem*. Many of these patients with vascular lesions do, however, have relatively high arterial pressure. Moreover, the experience of insurance companies has shown that mortality is related to arterial pressure, and that the excess mortality of those with the higher pressures is largely due to cardiovascular renal disease (page 180). Since arterial pressure is

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nearly always with a succession of happenings; the object that is the focus of our attention at some instant is merely the expression of the causal sequence at that time

To investigate such complex problems, we have the classical method of natural science: first, the accurate description of facts or events; second, their arrangement; and third the invention of a hypothesis to explain the relationship between them. This hypothesis is then tested by experiment, and by its ability to predict correctly other events. If the hypothesis withstands this test it achieves the status of a theory and finally, the dignity of a law. This process has been remarkably successful in dealing with the phenomena exhibited by inanimate objects, and in recent years with those exhibited by animate objects. But it has only had a limited success in elucidating the etiology of disease. One cause of this comparatively limited success is the enormous complexity, already noted, of the factors concerned. Another consideration that is generally overlooked is that medicine does not begin, as it were, with a blank page. An organized system of beliefs concerning the origin of disease, and of practices designed to prevent or cure it, existed long before the advent of what we now call natural science. Modern medicine has been fashioned by the scientific method out of an earlier creation deriving from magic and religion. To our ancestors disease was the reward of sin, and it is no accident that many of my teachers believed that high blood pressure and arterial disease were the result of eating too much, of drinking too much and of smoking too much. So far as I am acquainted with the evidence, it would seem that their treatment, which they firmly believed to be life saving, was quite ineffective in prolonging life in this world, but as it implied the mortification of the flesh, it is to be hoped that it met with greater success in the next.

Each step forward in science represents a simplification. Complex and hitherto apparently unrelated phenomena begin to fall into place after the development of an idea or hypothesis. It may be noted in passing that the actual hypothesis often represents an oversimplification, and subsequent work has to extend or modify it to relate it more closely to observed facts.
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The next
influential do individual factors seem to be until, when we reach the terminal stage, the causal agent seems to be in unique relationship with the ultimate effect. So may be portrayed the philosophy of a unique cause. But there is another way in which this philosophy operates. In attempting to isolate from the vast array of possible factors those that chiefly determine a particular happening, in this case a disease, we attempt to assign some estimate of importance, as it were a value,

easily and quickly measured, high blood pressure has become one of the conditions most frequently diagnosed by the doctor and dreaded by the patient. It has also been the chief focus of research into vascular disease partly, at least, because it seemed to be a problem that could be solved by the methods and techniques so successfully developed by physiology.

THE PROBLEM OF *Æ*IOLOGY

The challenge to medicine of vascular diseases and high blood pressure may be resolved into two questions: what can be done to prevent these conditions, and what can be done to mitigate their evil effects if they exist already? This brings us at once to the question of ætiology or the search for causes, for the success of modern science in controlling the forces of nature is based not on empiricism but on an understanding of what these forces are. What are the successive links in the chain of causation which bring about a raised arterial pressure or a particular kind of vascular disease? To what extent does the mere possession of this elevated arterial pressure prejudice the wellbeing of the individual, and do measures designed to reduce the arterial pressure improve the wellbeing or expectation of wellbeing? These are some of the questions which will be examined in later chapters of this book. Here we may consider briefly the problem of the ætiology of disease in general and some of the difficulties peculiar to our present topic.

The General Nature of the Problem

It is generally believed that the characteristics of any living creature are due to the interaction of two components, namely what he was born with and what has happened to him since he was born, or more strictly his genetic constitution as determined at the time of the conjugation of the germ cells and the impact on it of subsequent events; in other words, inheritance and environment. Reduced in this way to its bare essentials, the problem seems simple enough, but in fact each component is extremely complex, and their interaction even more so. To take a simple example, there are several thousand combinations of the known hereditary factors responsible for the phenomena of the blood groups, and new factors are still being discovered. As for environment, any incident, or combination of incidents, that have happened to us during our existence may be the relevant factors so far as a particular disease is concerned. If we remember, too, that our state may be determined not only by environmental agencies that operate on the body but also by those that operate on the mind, then we begin to realize the dimensions of the problem. We very seldom deal with anything so simple as a single cause or a single effect, but

discover the ultimate cause or mechanism. Nor have we been able to segregate these environmental and hereditary factors that may be concerned in setting into motion the causal sequence. It is for this reason, if for no other, that an essay of this kind must treat the subject broadly, for it is the spice of scientific enquiry that no one can foretell whence will come that vital fact or energizing idea that will enable those that have hitherto "seen through a glass, darkly" now to see "face to face."

In dealing with high blood pressure we meet other considerations which add greatly to the difficulty of our task, and which should be faced from the outset. I refer to the fact that high blood pressure is a symptom, not a disease. It is the resultant of a complex set of factors, and the resultant may be the same even though the relevant factors differ greatly in their individual magnitude. Moreover, it is not only the height of his blood pressure that is important to the present or future wellbeing of the individual, the associated organic vascular disease is of equal, and in many cases of greater, moment. These organic vascular diseases are also of various kinds; some seem to be

... FOR TWO REASONS. In the first place, understanding of the causal sequence has been hindered by the uncritical transfer of ideas gained from a study of one set of processes to another that is totally different; or by the supposition, as in essential hypertension, that we are dealing with a specific morbid process to which the philosophy of unique causation can be applied. In the second place, three hypotheses are presented here that represent attempts at simplification. This is not the first time that each has been presented separately; but I believe it is the first time that they have been presented together. And the reader is invited to consider to what extent they exchange some kind of order for the disorder that has hitherto prevailed, and to what extent they require modification in the light of existing knowledge that has been overlooked, or whose importance has been underestimated, and to what extent they will stand the test of future observation and experiment. These hypotheses will be fully presented in the relevant chapters of this book in the context of the matrix of evidence from which they crystallized. It does, however, seem worthwhile mentioning them at this stage before the reader becomes immersed in detail.

SOME OF THE MORE IMPORTANT PROPOSITIONS TO BE PRESENTED

The first proposition concerns the nature and pathogenesis of essential hypertension. Arterial pressure, like height, weight and other

to each. We can do this most confidently when we can pick out one and say this alone is important or, with less assurance, this is of major importance, these others are only contributory. Here we see the doctrine of unique cause, not so much as a description of the final event, but as a selection of the more relevant from the less relevant. Advances in our understanding of the mechanism of disease in the last century have been chiefly along these lines. Thus the germ theory of disease envisaged as the unique or causal event the invasion of the body by a particular microbe. To suppose, however, that the sole event determining infection is contact between microbe and host is a gross oversimplification. We now know that infection is caused not merely by the contact of the microbe and host but also by the number and virulence of the organisms, on the one hand, and by the inherited constitution, the emotional and nutritional state and degree of fatigue of the host on the other. Any of these may be the determining factor. To take a simple example, Pasteur showed that the fowl was naturally resistant to anthrax, yet if the body temperature of the fowl was reduced it might easily be infected and succumb to the microbe. Here we may regard exposure to anthrax as the unique cause, and yet it was the change in body temperature that was the determining factor in the result. The values that we assign to the various factors have thus no fixed and immutable character, but depend on circumstances.

The Special Difficulties presented by Vascular Disease and High Blood Pressure

It would seem that we understand causation only in those diseases in which a single factor is so clearly demonstrable and of such outstanding importance that it can be picked out with some certainty. Thus we know a good deal about those diseases that are due to the inheritance of a gene which behaves as a simple Mendelian dominant (e.g. Huntington's chorea) less about those that depend on recessive inheritance (perhaps Wilson's disease, hepato-lenticular degeneration, may be cited). We know much of the diseases due to invasion by the larger micro-organisms (protozoa and bacteria), less about those due to ultramicroscopic microbes or viruses. We know something about diseases due to the action of chemical substances taken in excess (e.g. lead poisoning) and to necessary bodily components ingested in defective amounts (scurvy, iron deficiency anaemia). When, however, we have discerned the unique cause, as in iron deficiency anaemia, we find a considerable variety of inherited and environmental factors (gastric secretion, diet and blood loss) whose conjunction is necessary to bring it about.

In some of the commonest diseases of civilized society, the rheumatic diseases, cancer and vascular diseases, we have as yet been unable to

countries, and will be used frequently in this book. The temptation to use it as a title was, however, deliberately resisted for two reasons. First, it is not a very well chosen word, a bastard of Greek and Latin parentage, and signifying not high blood pressure but over-much stretching. Secondly, the use of the term has led to the practice of distinguishing between normal blood pressure and hypertension, and thus by easy stages to the assumption that those subjects with hypertension necessarily differ qualitatively from the rest of mankind; a conception which has been fatal to an appreciation of the factors concerned in the pathogenesis of essential hypertension.

measurable characteristics, shows a curve of continuous variation¹ in the population at large. Unlike height, the distribution curves are very different at different ages after adolescence is finished, and the average values for arterial pressure tend to rise steeply in the older ages. It seems that essential hypertension represents little, and perhaps nothing, more than the upper end of the distribution curve, designated as essential hypertension at some arbitrary level such as 150 systolic, 100 diastolic. On this view, the difference between subjects with essential hypertension and those with lower pressures is quantitative and not qualitative, a matter of degree, not of kind. And it is suggested that essential hypertension is the resultant of the interaction of genetic and environmental factors that operate in the population at large. Of these, the influence of age and inheritance can be defined approximately. Environmental factors are probably of even greater importance, but their rôle individually remains uncertain.

The second proposition is that, when arterial pressure is raised for long enough by some specific interference, then the arterial pressure may remain relatively high when the original specific interference is removed. This proposition is derived from experiments with animals and is supported by the results of experiments done in man in the form of therapeutics. This proposition may be of great importance particularly in relation to the possible rôle of environmental factors in essential hypertension.

The third proposition is that the malignant phase of hypertension is a consequence of the degree to which arterial pressure is elevated and the speed with which that elevation was attained. The malignant and benign phases of hypertension thus express differences in degree, not of kind. The occurrence of the malignant phase probably partly accounts for the observed fact that there is a ceiling above which arterial pressure does not rise. The importance of this hypothesis to therapeutics needs no emphasis.

These three propositions form, as it were, the skeleton of a concept of essential hypertension about which many of the previously discovered characteristics seem to achieve some orderly arrangement. It is to be emphasized, however, that they are in the stage of hypothesis and may require revision, amendment or total repeal in the light of future knowledge.

TERMINOLOGY

High blood pressure has a number of equivalents in the technical jargon of the day: *hyperpiesia*, *hypertonia*, and *hypertension*. Of these, the last is by far the most prevalent in the English-speaking

¹ In the case of arterial pressure, this is not a "normal" curve. For fuller discussion see Chapter 8.

wave is reflected back and may summate or interfere with the oncoming wave. Thus, it has been suspected by indirect measurement in man that the systolic pressure recorded from the femoral artery may be higher than that recorded from the brachial, even though leg and arm are at the same level. This is particularly true in aortic regurgitation (Hill and Rowlands, 1912). Direct measurements of arterial pressure with high frequency optical systems show that in the dog the systolic pressure is usually higher in the brachial artery than the aorta.

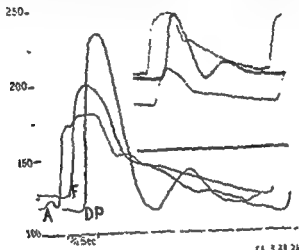


FIG 2.1. Axillary, femoral, and dorsalis pedis artery pressure records in man. (Hamilton, Woodbury and Harper, 1936, Fig. 2.1.)

Fig 2.1, from Hamilton, Woodbury and Harper (1936), shows three simultaneous optical records of blood pressure from the axillary artery, femoral artery and dorsalis pedis artery in man. The systolic pressures were severally 165 mm Hg¹ in the axillary, 200 mm. Hg in the femoral and 235 mm Hg in the dorsalis pedis artery. In fact, as Hamilton (1944) has pointed out, the form of the pulse, and thus the systolic and diastolic pressures, differ greatly in the various arteries of the same animal at a given instant, due to the complex summation and interference of waves and reflected waves. In the dog, the aorta shows a great standing wave whose node oscillates around a point in the lower thoracic aorta. The reflected wave and therefore the systolic and diastolic pressures in an artery are much influenced by the state of contraction or dilatation of its branches.

¹ This is the figure given by these authors, but I should judge from Figure 2.1. that 187 mm. would have been more nearly correct.

CHAPTER 2

MEASUREMENT OF ARTERIAL PRESSURE IN MAN

THIS book is concerned with arterial pressure in man. It seems important therefore to consider what it is that we measure when we estimate the arterial pressure, and how accurate these measurements are.

TRANSMISSION OF THE ARTERIAL PRESSURE PULSE : SYSTOLIC, DIASTOLIC AND MEAN PRESSURES

The sudden distension of the aorta at the beginning of the ejection phase of ventricular systole produces a pressure wave which travels along the aorta and its branches, both in the wall of the vessels and the fluid inside. After this wave, the pressure falls to a minimum. As the wave traverses the subdividing vascular tree, it becomes smaller and finally dies out in the capillaries, unless the pulse pressure is high and the arterioles dilated, when it reaches the venules as so-called capillary pulsation (Lewis, 1924). The rate of propagation of this wave is used to measure elasticity of the arterial wall (Bramwell, Downing and Hill, 1923).

At any point in the arterial system it is possible with a manometer of high frequency and small displacement to record two values of pressure, a minimum, or diastolic, and a maximum, or systolic. By choosing a manometer of very low frequency, such as a wide-bore mercury manometer, it is also possible to measure a mean pressure. In clinical medicine what we measure ordinarily as arterial pressure are approximations to the systolic and diastolic values. What the physiologist measures with his arterial cannula and wide mercury manometer is an approximation to mean pressure. So far as the flow of blood is concerned, mean pressure is probably a more useful figure than either the systolic or diastolic values. Mean pressure cannot be simply deduced from the systolic and diastolic figures. It is necessary also to know the shape of the pulse wave and to integrate pressure in respect of time. Mean pressure would only be half the sum of systolic and diastolic values if the pulse curve was of triangular shape. In fact, it is always concave upwards, but the shape of the concavity is not uniform, and there are many component smaller waves and curves. As a rule, mean pressure is nearer diastolic than systolic.

While it is probably true to say that mean pressure falls steadily, though not uniformly, as the blood passes along the aorta and through its branches, the relation of systolic and diastolic pressures is much more complex, owing to the fact that at each subdivision a pressure

thumbscrew, the pressure itself being recorded in ounces of troy weight on the adjacent dial. These clumsy instruments were also very inaccurate. They were, however, the forerunners of several others

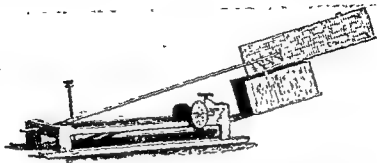


FIG 2 3 Mahomed's sphygmomanometer. The pulse is inscribed by a lever writing on the clockwork drum to the right of the figure. Next to the drum is a thumbscrew which adjusts the pressure required to obliterate the pulse, the pressure being recorded on the dial in ounces of Troy weight.

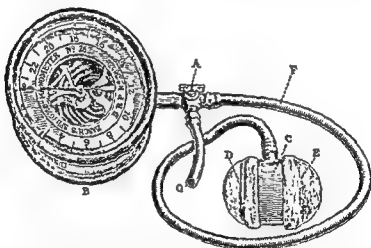


FIG 2 4. Von Basch's sphygmomanometer as eventually developed for use at the bedside. A is a stopcock by which the pressure can be adjusted. The bulb is used to compress the radial artery over the brachial artery on the upper arm.

designed to compress the radial artery until the distal pulse could no longer be felt. Of these, by far the most practicable and generally used was that of von Basch (Fig. 2.4). The intervening instruments are described and discussed by Brunton (1908), Master, Garfield and Walters (1952).

INDIRECT METHODS OF MEASURING ARTERIAL PRESSURE

Almost the whole of our present knowledge of arterial pressure in healthy and diseased man is based on determinations by indirect methods. The last century witnessed a long succession of instruments designed for this purpose, beginning with that of Hérissou in 1834 (Fig. 2.2). Hérissou's apparatus consisted of a metal hemisphere sealed on its plane surface with a flexible membrane and carrying a graduated capillary tube at its summit. The apparatus was filled with mercury to part way up the capillary. When placed over the radial artery, the pulsations were transmitted to the capillary where they

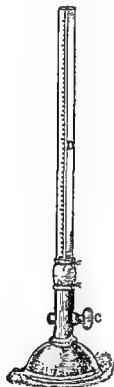


FIG. 2.2. Hérissou's sphygmomanometer. The funnel closed with a thin membrane at its larger end contains mercury. The membrane is placed over the radial artery and the apparatus is pressed down till the pulse stops. The height of the mercury column in the capillary tube is read on the scale. [Figs. 2, 2, 4 and 5 from Brunton's "Therapeutics of the Circulation," John Murray.]

could be measured. Although the purpose of this instrument was to measure the amplitude of the pulse, it could be used incidentally to measure the arterial pressure and was so used by later workers.

The first apparatus specifically designed to measure arterial pressure was that of Vierordt in 1854, in which weights were applied to a scale pan until the pulse compressed by a button was obliterated as shown by cessation of the movement of a writing point. Mahomed's instrument (Fig. 2.3) was a modification of Vierordt's and is of great interest because it enabled that luminous mind to appreciate the main features of what we now know as essential hypertension some twenty years before his time (see Chapter 6). In this instrument, the pressure on the button compressing the radial artery was adjusted by a

pressure, while the point at which they were suppressed represented systolic pressure.

Out of the two lines of evolution have developed the modern methods of measuring the blood pressure. The first important advance was in 1896 by Riva-Rocci, who inflated a pneumatic cuff on the upper arm to a pressure sufficient to obliterate the pulse at the wrist. Later v. Recklinghausen (1901) showed that Riva-Rocci's arm band gave erroneously high readings and recommended a cuff 10-15 cm. wide. In 1905, Korotkoff, a Russian physician, suggested that the sounds heard over the artery distal to the cuff should be used as indices of systolic and diastolic pressure. Subsequent work showed that those sounds passed through four successive phases as the arterial pressure was reduced.

Phase I. Sudden appearance of a clear, but often faint, tapping sound growing louder.

Phase II: The sounds are prolonged into a murmur.

Phase III: The sounds become clearer and increase in intensity.

Phase IV. The sounds quickly decrease in intensity and finally disappear.

It is of considerable interest that the two papers on which contemporary methods of estimating blood pressure are based, are inaccessible to most readers in the English-speaking world. W. Hall Lewis (1941) states that in the United States the only copy of Riva-Rocci's paper is in the Army Medical Library, and the only copy of Korotkoff's report is in the Slavonic Division of the New York Public Library.

Lewis obtained translations of both papers, and I quote him as follows.

Riva-Rocci first recorded the purpose of his research on arterial pressure and then set forth the simpler aspects of his work.

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Meanwhile, an entirely different principle had been introduced by Marey in 1878. The forearm was enclosed in a plethysmograph containing water, whose pressure was raised until the pulsations of the water, recorded on a drum, became maximal. Marey considered that at this point the pressure in the plethysmograph exactly balanced the pressure of the blood inside the arteries. This pressure therefore



FIG. 2.4. Marey's sphygmograph. The tubes E are filled with water

represented the true internal pressure of the arteries. Marey and his pupil, Mosso (1895), diminished the size of the instrument by enclosing either one or four fingers in the plethysmograph. The former was insensitive, the latter (Fig. 2.5) scarcely portable. Moreover, views concerning the significance of the pulsations changed so that it became accepted that, as the pressure was raised, the point at which the plethysmographic pulsations became maximal represented diastolic

He suggested an armlet 13 cm. broad and 30 cm. long as the most generally suitable. While there has been general agreement that the first sound appears when the cuff pressure represents systolic, the diastolic value has been more controversial. Most people have found the junction between phases III and IV, that is to say, the point at which the sounds abruptly fade, the easiest to recognize; and it has theoretical affiliations to the point of maximal pulsation of the plethysmograph. The joint committee of the American Heart Association and Cardiac Society of Great Britain and Ireland in 1939 hesitated on this point, for while they agreed that the beginning of phase IV should be accepted as the diastolic pressure, they considered that, if the sounds disappeared at a lower pressure, this should also be recorded. In 1951, the Committee set up by the American Heart Association concluded that the point of complete cessation of sounds is the best index of diastolic pressure (Bordley, Connor, Hamilton, Kerr and Wiggers, 1951). In all the work done by me and my associates the point at which the sounds abruptly begin to fade has been taken as diastolic pressure.

A mercury manometer is now very generally used to measure the pressure in the cuff which is inflated with a small hand-pump and deflated by a needle valve. Other forms of pressure gauge are not recommended, since their calibration alters and they may be quite inaccurate.

The accuracy and limitations of the auscultatory method of determining blood pressure will be more fully discussed on p. 17. Here two sources of error may be noted. The first is the auscultatory gap. As the pressure is reduced during phase I, the sounds become fainter and disappear, to reappear again some millimetres lower. This has been studied by Ragan and Bordley (1941) and appears to be influenced by the rate of inflation and deflation of the cuff, and thus by the residual pressure in the vessels distal to the cuff after arresting the circulation. The importance of this phenomenon is that the cuff must be inflated well above systolic pressure if a false reading of systolic pressure is not to be obtained. The second phenomenon occurs in aortic regurgitation, arterio-venous fistula and other conditions associated with a water-hammer, Corrigan or "collapsing" pulse and therefore with a large pulse pressure. In such circumstances, there may be no clear separation between phases III and IV, and a loud sound is audible over the brachial artery, even though the cuff pressure is zero. This is the well-known pistol shot sound of Duroziez, and is probably produced by the deformation of the artery by the stethoscope itself. Under such circumstances, the diastolic pressure and the transition from phase III to phase IV cannot be defined.

On the Continent of Europe the arterial pressure is measured

in action, precise, and innocuous. It was composed of two parts, one for exerting pressure, one for measuring the pressure exerted. The compressor apparatus was represented by a tubular "muff" with walls soft, non-extensible, and impermeable to air. It consisted of a rubber tube 4 or 5 cm. in diameter, lined with a cloth sleeve to prevent undue dilation of the tube. One end of the tube was open, while the other was attached to a piece of metal made in two parts. The patient's arm was tested with this tube plus an insufflator. The intercalation of a manometer revealed the pressure on the "muff" at all times, and hence the pressure exerted on the arm.

Riva-Rocci stated: "The most reliable manometer is still the mercury manometer, but it is necessary to facilitate its reading by adopting a single

construction."

... Korotkoff's observations were given at a meeting of the Imperial Military Academy in St. Petersburg, December, 1905 and reported in the bulletin of the Academy, "Izvestiya Voennomeditsinskoi Akademii," page 365. The original report occupies only a portion of one page in the bulletin, with the title: "On methods of studying blood pressure (from the Clinic of Prof. Feodoreff)." A translation in full reads:

"On the basis of his observation, the speaker came to the conclusion that a perfectly constricted artery, under normal conditions, does not emit any sounds. Taking this fact into consideration, the speaker proposes the sound method for measuring blood pressure on human beings. The sleeve of Riva-Rocci is put on the middle third of the arm; the pressure in this sleeve rises rapidly until the circulation below this sleeve stops completely. At first there are no sounds whatsoever. As the mercury height, there appear the first short or indicates that part of the pulse wave of sleeve. Consequently, the reading on the manometer when the first sound appears corresponds to the maximum blood pressure; with the further fall of the mercury in the manometer, there are heard systolic pressure murmurs which become again sounds (secondary). Finally all sounds disappear. The time of

positive results. The first sound tones appear (10-12 mm.) sooner than the pulse which (l. ar. radialis) can be felt only after the passage of the major portion of the blood stream."

There were now available three methods of determining the arterial pressure from the inflation of a cuff on the upper arm; the suppression of the pulse as felt at the wrist, the Korotkoff sounds, and the pulsations of the air contained in the cuff. Many papers have been written on these methods and their variations, their sources of error, accuracy, and convenience (see for example v. Recklinghausen's series in 1906 and 1930). In the English-speaking world the auscultatory method has come to be almost the only method used. Von Recklinghausen pointed out that the use of too small a cuff gave erroneously high readings, while the use of too large a cuff gave erroneously low readings.

1 This should read *Izvestiya Imperatorskoi Voenno-Meditsinskoi Akademii*.

ordings ; it would be presumptuous for one without direct experience to pass judgment. Some remarks are, however, apposite. In using the optical capsules, it is necessary to use a wide arterial needle and to connect this to the capsule with a lead tube, the whole being filled with sterile saline containing heparin. The records obtained can be of great accuracy, but the subject is restrained by the rigidity of the apparatus. The strain gauge is one of the simplest to use, and it can be connected with the arterial lumen by a thin flexible nylon catheter ; but its frequency is low, and the accuracy of its records of systolic and diastolic values in central arteries doubtful. The capacitance manometer can be fitted to a short saline-filled intra-arterial needle which is trapped in position on the limb. The flexible leads pass to the amplifying and recording system. Its accuracy is high and its usefulness is being generally acknowledged.

All these methods of direct recording of arterial pressure involve intricate apparatus, and careful attention to detail if accuracy is to be achieved. For this reason alone they must for many years be research instruments only, and for our present purposes their chief importance is the light they throw on the validity of the indirect records.

COMPARISON OF DIRECT AND INDIRECT MEASUREMENTS OF ARTERIAL PRESSURE IN MAN

The first comparison of pressures measured by direct methods just described and indirect methods was by Wolf and v. Bonsdorff (1931). The pressure was measured directly from one brachial artery by inserting into it a needle connected through a saline-filled lead tube to Brömser's glass membrane manometer recording optically. Blood pressures were measured from the other arm by the auscultatory method, and by Flesch's tonometer, before, during and after the direct measurement. The cuff size was not stated. They observed considerable differences between the pressures measured indirectly by both methods and the true values, and they considered that, while the indirect method gave a correct appreciation of the order of pressure, it was so inaccurate that small differences were of no significance. Von Bonsdorff (1932) later summarized the results of the comparison which are shown in Table 2.1. The systolic and diastolic readings measured indirectly come within 5 mm. of the values obtained directly in less than half the cases.

In 1936 Hamilton, Woodbury and Harper compared the brachial artery pressure measured directly by the optical capsule and indirectly by the auscultatory method. The indirect measurements were on an average 3-4 mm. too low for systolic and 9 mm. too high for diastolic using " fading of the fourth phase " They concluded that their results indicated " that the indirect method agrees reasonably well with the

determined by an oscillometer, in which the cuff is connected to a high-frequency type of pressure gauge. One of the best known of these is Pachon's oscillometer (Pachon, 1909), now commonly used with Gallavardin's double cuff, an upper and a lower, connected to the two sides of a high-frequency diaphragm type of pressure gauge. The oscillations of the diaphragm record the volume change of the main artery of the limb transmitted to the air in the cuff.

Another type is Plesch's tonoscillometer (1930), in which two elastic manometers of different sizes are used respectively to record the pressure in the cuff, and its pulsations. In both these types of apparatus, as in the earlier plethysmographs, the first pulsation occurring as the pressure is reduced is held to occur at systolic pressure, the maximum pulsation at diastolic pressure.

DIRECT MEASUREMENT OF ARTERIAL PRESSURE IN MAN

The arterial pressure was first measured directly in man in 1856 by Faivre. He connected a Poiseuille mercury manometer to the femoral artery in one, and to the brachial artery in two, patients before the amputation of the limb. He thus measured an approximation to mean pressure which he found to be about 120 mm. Hg. In the present century much attention has been devoted to the construction of manometers suitable for the accurate recording of systolic and diastolic pressures. Frank in 1903 laid down the principles that should govern the construction of a manometer for this purpose, particularly high frequency of response and small displacement of the moving parts. He devised a segment capsule in which the movements of a tightly-stretched rubber diaphragm were recorded optically by a small plane mirror fixed to one side. This was developed by Wiggers, by Brömser (1928), who used a thin glass membrane, and by Hamilton (Hamilton, Brewer and Brotman, 1934), who used a thin metal diaphragm. Other devices since developed are as follows:

(1) The capacitance manometer in which the membrane forms one plate of a minute condenser, particularly developed by Tybjaerg Hansen and Warburg (1947).

(2) The piezoelectric manometer described by Langevin and Gomez (1933).

(3) The photoelectric manometer of Rein (1940).

(4) The mechano-electric transducer valve of Pettersson and Clemedson (1950).

(5) The strain gauge, in which the movements of the membrane are transmitted to strain sensitive wires which form either one arm (Grundfest, Hay and Feitelberg, 1945) or opposite arms (Lambert and Wood, 1947) of a Wheatstone bridge.

Many laboratories are now experimenting with these methods of

with a cuff 4-6 cm. wide, but good agreement when a cuff 2-5 cm. wide was used. They point out, however, that the form of the pulse wave in the umbilical artery differs from that in the brachial. In 1939 Robinow, Hamilton, Woodbury and Volpitta compared direct readings from the brachial artery with simultaneous indirect readings by auscultation in 62 infants and children aged six weeks to 13 years.

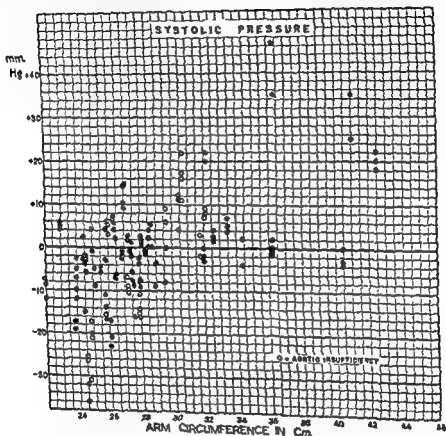


FIG. 27 Deviation of auscultatory measurements from intra-arterial measurements of systolic pressure in relation to arm circumference (Ragan, C and Bordley, J., III (1941), *Bull. Johns Hopk. Hosp.*, 69, 504).

They used cuffs 2.5 cm., 4.5 cm., 6.5 cm., 9 cm. and 11 cm. broad and took diastolic pressure at the beginning of the fourth phase. In each case a certain width of cuff gave a value for systolic pressure which agreed with that measured directly.

... was better if the diastolic ... calculated as a percentage of the indirect systolic reading than

TABLE 2.1. *Comparison of the Arterial Pressure Measured Directly by a Frank Capsule and Indirectly using the Korotkoff Sounds (v. Bonsdorff, 1932).*

		No. of Patients	
		Systolic Pressure	Diastolic Pressure
Korotkoff value too high	>20 mm.	1	1
	20-10 mm.	0	5
	10-5 mm.	6	2
No difference	Within ± 5 mm.	9	11
Korotkoff value too low	5-10 mm.	6	5
	10-20 mm.	2	1
	>20 mm.	1	0

direct method." In 1938 Woodbury, Robinow and Hamilton compared the pressure measured directly from the umbilical artery and from the brachial artery measured indirectly by palpation in infants at birth. The direct method gave higher readings than the indirect

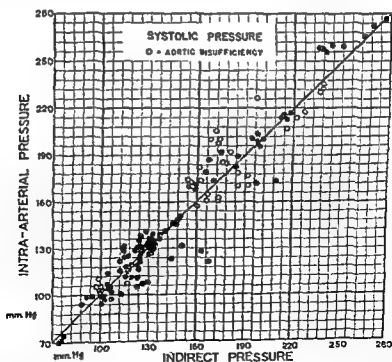


FIG. 2.6. Correlation between auscultatory (indirect) and intra-arterial measurements of systolic pressure (Ragan, C. and Bordley, J., III (1941), *Bull. Johns Hopk. Hosp.*, 69, 504).

pressures estimated by the auscultatory method did not differ by more than 2 mm. in the two arms. Fig. 2.6 shows the correlation of the two methods of measuring systolic pressure. Fig. 2.7 shows the deviation of the pressures in relation to the size of the arm. In the two arms the values are low; with small arms the values are low; with large arms they are not the only

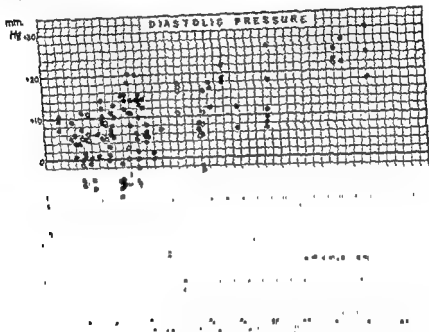


FIG. 2.8. Deviation of auscultatory measurements from intra-arterial measurements of diastolic pressure in relation to arm circumference (Ragan, C and Bordley, J., 1941, *Bull. Johns Hopk. Hosp.*, 69, 504.)

cause of the discrepancy and the authors attributed the remainder largely to the shape of the pulse wave.

Fig. 2.8 shows the correlation between direct and indirect values for diastolic pressure, and Fig. 2.9 the relation of the deviation of the indirect readings to circumference of arm. Ragan and Bordley made no statistical analysis of their results, but from their published data Pickering, Roberts and Sowry (1954) calculated the relationship between the difference of direct and indirect measurement and arm circumference. From these calculations, they prepared a table (Table 2.2) to show the corrections for arm circumference to be applied to auscultatory measurements of arterial pressure. They pointed out that these corrections are worth making where large groups of indivi-

with the actual indirect determination of diastolic pressure. They concluded that, while it is possible to estimate the systolic pressure accurately by auscultation in children provided the proper cuff width is selected, the diastolic is of limited value. How artificial these comparisons are is indicated by their observation that inflating a cuff distal to the arterial needle profoundly alters the pulse form, raising both systolic and pulse pressures, while inflating a cuff on the other arm is without effect. Clearly here we are dealing with complex

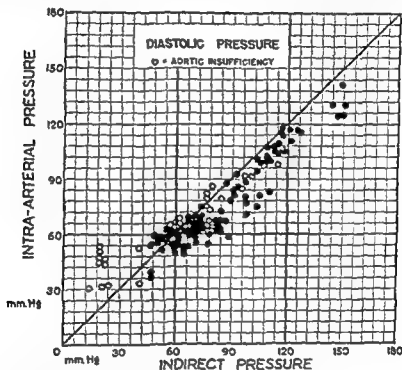


FIG. 2.8. Correlation between auscultatory (indirect) and intra-arterial measurements of diastolic pressure (Ragan, C. and Bordley, J., III (1941), *Bull. Johns Hopk Hosp.*, 69, 504).

effects of the pulse-wave and its reflection. Juggling with cuff width will give a reading for systolic agreeing with that estimated directly from an artery in which the pulse wave is quite different and has an unknown relation to that in the aorta.

An investigation into the effects of arm size on the errors of indirect measurement was reported by Ragan and Bordley in 1941. They measured simultaneously the pressures obtained directly by a Hamilton manometer from one brachial artery with the pressures recorded by the auscultatory method from the other arm using cuffs 13 cm. and 20 cm. wide. They investigated 51 adults, 28 with normal or low pressures, 12 with hypertension and 11 with aortic insufficiency. In all of these subjects preliminary investigation had shown that blood

pressures estimated by the auscultatory method did not differ by more than 2 mm in the two arms Fig. 2.6 shows the correlation between the direct and indirect methods of measuring systolic pressure using a cuff 13 cm. wide for the indirect method. Fig. 2.7 shows the deviation of the pressure by indirect measurement in relation to the size of the arm Here a definite trend becomes apparent ; with small arms the values by indirect measurement tend to be too low ; with large arms they tend to be too high. This, however, is not the only

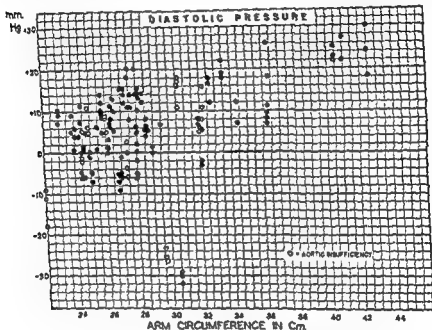


FIG. 2.8 Deviation of auscultatory measurements from intra arterial measurements of diastolic pressure in relation to arm circumference (Ragan, C. and Bordley, J., III (1941), *Bull. Johns Hopk. Hosp.*, 69, 504)

cause of the discrepancy and the authors attributed the remainder largely to the shape of the pulse wave.

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22 MEASUREMENT OF ARTERIAL PRESSURE IN MAN

TABLE 2.2. *Corrections for Arm Circumference to be Applied to Auscultatory Measurements of Arterial Pressure. (Based on data from Ragan and Bordley (1941).)*

Arm circumference to nearest cm.	Systolic Pressure mm. Hg	Arm circumference to nearest cm	Diastolic Pressure mm. Hg
15-18	Add 15	15-20	No correction
19-22	Add 10	21-26	Subtract 5
23-26	Add 5	27-31	Subtract 10
27-30	No correction	32-37	Subtract 15
31-34	Subtract 5	38-43	Subtract 20
35-38	Subtract 10	44-47	Subtract 25
39-41	Subtract 15		
42-45	Subtract 20		
46-49	Subtract 25		

duals are concerned. In single individuals the corrections are probably not worth applying, since variations in arm circumference account for no more than a quarter of the differences between direct and indirect readings.

Rather similar results were reported by Steele (1942), who compared direct and indirect readings in 39 individuals, the direct readings being taken from the radial artery. Indirect measurements underestimated systolic pressure by an average of 10 mm. Hg and overestimated diastolic by 8.8 mm. Hg, if the sudden muffling of the sounds were taken and by 1.3 mm. Hg if disappearance of the sounds were taken as the index.

COMMENT

At the present time, for routine clinical use, there seems no practicable alternative to the indirect methods of measuring blood pressure. What the direct methods gain in accuracy they lose in complexity and in the disturbance to the patient, which, as we shall see, has an important effect on arterial pressure. Even direct methods estimate only the maximal and minimal values for that artery at that site. In different arteries and in the aorta the values may differ very considerably. Thus, if we hope to obtain information as to systolic and diastolic pressures in the aorta, we cannot accept as reliable indices the values measured by the most accurate manometers from the brachial, radial or femoral arteries.

The auscultatory method is probably the best and most convenient of the indirect methods. A mercury manometer should always be used; the mercury should be clean; the top of the column should have a free connection with the atmosphere and the zero should be checked.

The systolic value is best indicated by the first appearance of the sounds, the diastolic value by their final disappearance. Nevertheless, the point of abrupt diminution in sound is more easily ascertained, and is still the accepted index of diastolic blood pressure in Great Britain and most other countries. In adults a cuff 13 cm. broad and 30 cm. long is recommended. In general the results so obtained will underestimate systolic and overestimate diastolic pressure in adults of normal weight, while in the very obese both values will be overestimated. This consideration becomes important when we consider the relation between obesity and arterial pressure.

The fallacies inherent in the measurement of arterial pressure should make us look rather sceptically at conclusions drawn from readings on single individuals.

The matters discussed in this chapter leave the writer with a sense of chastened humility. The methods we use to estimate blood pressure are obviously of limited accuracy, and the values we seek to record, systolic and diastolic pressures, have themselves an elusive quality. The moral, however, would seem clear, that we should not attach too much importance to the precise figures obtained in the individual subject, and that in grouped figures we should try to detect any systematic source of error in the readings obtained.

CHAPTER 3

DIURNAL VARIATIONS IN ARTERIAL PRESSURE. THE IMMEDIATE RESPONSES TO ENVIRONMENTAL CHANGES

DIURNAL VARIATIONS AND THE EFFECTS OF SLEEP

LIKE so many other measurable characteristics, the arterial pressure is subject to considerable variations during the course of the twenty-four hours. The full extent of these variations and the factors determining them will probably not become fully apparent until continuous records with a recording manometer attached to a small intra-arterial cannula have been obtained. Technical difficulties, connected particularly with clotting in the cannula and the recording devices themselves, preclude this at present. Nevertheless, much information has been obtained by the indirect method.

From measurements by the indirect method it would seem that in a resting subject the systolic pressure shows a gradual rise from early morning to a maximum between 5 and 7 p.m., with slight and transient increases lasting fifteen to forty-five minutes after meals (Erlanger and Hooker, 1904; Brooks and Carroll, 1912 and Weyssse and Lutz, 1913). The diastolic pressure shows much less conspicuous variations than the systolic.

The blood pressure during sleep was much studied by the plethysmographic method and by the successive methods used to estimate blood pressure, largely because of a theory that sleep was due to cerebral anæmia (see Howell, 1897). Brooks and Carroll (1912), using the palpatory method, found that the blood pressure fell during the first two hours of sleep, and that the pressure remained at a low level for some hours after waking. The fall amounted to 20 mm. or more in most subjects. The drop was in some way connected with sleep, for it did not occur when sleep was prevented; while in night-workers the arterial pressure was higher at night when they were awake than in the day when they were asleep. Nevertheless, they concluded that the fall of arterial pressure was not concerned in the causation of sleep, since it was subsequent to, rather than preliminary to, or concurrent with, sound sleep. They studied 68 patients with medium blood pressures averaging 142.5 mm., 30 with low pressures averaging 100 mm., and 29 with high pressures averaging 204.5 mm. Hg systolic. The blood pressure fell during sleep in all subjects, but the fall was greatest in those with the highest and least in those with the lowest

initial pressures. Mueller and Brown (1930) described the results of hourly estimations of blood pressure for twenty-four hours in 26 normal subjects and 61 subjects with hypertension. The pressure gradually rose during the day to a maximum at 6-7 p.m. and then fell to reach a minimum between 3 and 4 a.m. The variations in subjects with hypertension occurred at the same time and were in the same direction as in normal subjects, but they were larger. In normal subjects the greatest variation of systolic pressure during the twenty-four hours was 65 mm. Hg, the least 15 mm. and the average 36.5 mm. Hg. In hypertension the corresponding figures were 120 mm., 25 mm. and 55 mm. Hg.

Muller (1921) made a similar study obtaining the systolic pressure by palpation, the diastolic by Hill and Barnard's oscillometric method, in subjects during sound sleep induced if necessary by veronal. He took the lowest reading obtained during the day and compared it with the lowest recorded at night. The night pressure was invariably lower than the day. He found that in children up to 14 years, both day and night pressures rose with age. After 14 years there was no further rise with age in night pressure (or day pressure) until the age of 45; but his groups were so small as to make this finding, which is at variance with those of other workers, of doubtful significance. In subjects with hypertension the fall during sleep was larger, and the size of the fall was roughly proportional to the degree of hypertension. Muller observed some patients in whom the fall of pressure during the night was reduced and in whom the night pressure, though not the day pressure, was higher than normal. He proposed that this group be termed "latent hypertension." Muller's mean figures for the lowest night and day systolic pressures are shown in Table 3.1. The numbers in each age group ranged from seven to 21. It is to be noted that patients in the older age groups with systolic pressures of 140 or over were excluded as hypertensive.

TABLE 3.1.

	Men				Women			
Age .	16-25	26-35	36-45	46-90	16-25	26-35	36-45	46-72
Day pressure	122	120	117	120	107	109	108	126
Night pressure	95	95	94	103	68	87	89	109

Katsch and Pansdorf (1922) studied the behaviour of the arterial pressure recorded by auscultation during sleep. They agreed that the systolic always fell, but the diastolic fell less and might rise. They noted that in hypertension there was a large fall during sleep, except

in association with anæmia, where there might be none. Campbell and Blankenhorn (1925) found a fall of pressure in sleep in normal subjects, but observed that in hypertension the fall was usually less.

MacWilliam (1925) agreed with these observations as regards sound sleep. But he stated that in disturbed sleep there might be a remarkable rise, for example of systolic from 125 to 182 mm. or 130 to 200 mm. and of diastolic from 75 to 105. "These changes were much greater than were induced in the same individuals by moderate exertion (cycling, walking, stair climbing, etc.), straining abdominal efforts, dose of atropin to remove vagus control over the heart, mental excitement, etc." No other observer has reported similar findings,¹ but the potential importance of these changes in connection with cardiac asthma is obvious, particularly since MacWilliam states: "The above-mentioned disturbances may occur during disturbed sleep when there is after awaking no recollection of definite dreaming."

Plethysmographic records from the upper extremity show that there is usually a vasodilatation of the skin vessels during sleep (Howell, 1897). The cardiac output is much more difficult to estimate. Grollman (1932), using his acetylene method, determined the cardiac output in the first few seconds after awakening, and after the subject was fully awake at hourly intervals during the night. He found both cardiac output and arterial pressure fell to low levels after the subject had fallen asleep, and remained low during the night, but that there was no consistent difference between the values obtained just after awakening and those obtained when the subject was fully awake. He stated "*There is thus no specific change in the blood pressure which is associated with the sleeping state, but the observed values occur irrespective of whether the subject is asleep or awake, so long as he is completely at rest.*"

It would seem therefore that the diurnal changes in arterial pressure, which, as has been noted, affect systolic more than diastolic, are partly to be attributed to changes in cardiac output, and partly to changes in vasomotor tone.

SENSORY STIMULI

It is common knowledge that most strong sensory stimuli produce a rise in arterial pressure and a quickening of the pulse rate. A loud

¹ MacWilliam refers to an earlier paper (1923) in which he describes three subjects the ages of 30 and 65.

noise, a bright light, cold applied to the skin, a needle prick, a burn, the perforation of a peptic ulcer and other painful experiences may be cited. Most of the stimuli produce cutaneous vasoconstriction, which, as Hallion and Comte (1894) showed, is probably reflex in origin, since its latent period is short, and repeated exposure to the stimulus is accompanied by a progressive diminution in response. This reflex is probably effected through the sympathetic nerves, since in some of these instances it has been shown that the response does not occur in the sympathectomized limb. However, it is possible that adrenaline is also released. Such stimuli as have been studied also produce a rise in cardiac output. A strong sensory stimulus, the effects of which have been much investigated in relation to hypertension, is the so-called cold pressor test to immersion of the hand in ice-water. This will receive attention in Chapter 7.

Reflexes from the Bladder

It is not generally realized how frequent and important are the rises of arterial pressure resulting from distension of the bladder. A patient who is lying quietly in bed may show a rise in arterial pressure

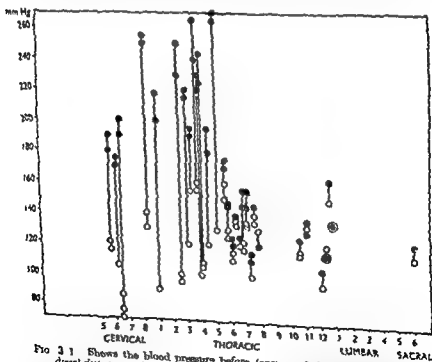


FIG. 31 Shows the blood pressure before (open circles) and after (black dots) distension of the bladder in a series of patients with transection of the spinal cord at the level shown (Guttmann and Whitteridge (1947), *Brain*, 70, 361).

in association with anæmia, where there might be none. Campbell and Blankenhorn (1925) found a fall of pressure in sleep in normal subjects, but observed that in hypertension the fall was usually less.

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ization, and arterial pressure with a capacitance manometer connected to an intra-arterial needle. They show that tilting a subject from the supine to the erect posture has little effect on arterial pressure, despite a fall in right auricular pressure and cardiac output; the blood flow through the upper limb decreases (Fig. 3.2) but is unchanged if the limb is sympathectomized.

It seems clear that the maintenance of arterial pressure during the change from the supine to the erect position is ordinarily achieved by vascular reflexes, possibly initiated by the baro-receptors of the carotid

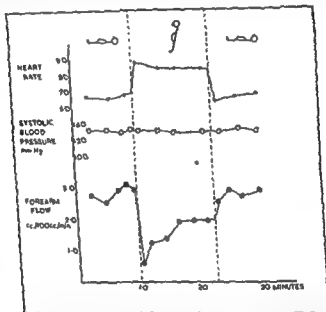


FIG 3.2. The heart rate, systolic arterial blood pressure (measured directly from the brachial artery with condenser manometer) and forearm blood flow during change from the recumbent to the head-up position on a tilting table (Brigden, Howarth and Sharpey-Schafer (1950), *Clin. Sci.*, 9, 79).

sinus and depressor reflexes (page 52), and effected through the sympathetic nerves. These reflexes counteract the effects of the large rise of hydrostatic intravascular pressure below the heart, and the reduction in cardiac output. As is to be expected when the effector fibres are interrupted temporarily by spinal anaesthesia or the ganglionic blocking action of hexamethonium salts, or permanently by lumbar dorsal sympathectomy, a profound fall of arterial pressure occurs (page 52) may be

...there is a profound fall of arterial pressure on assumption of the erect posture (postural hypotension (Bradbury and Eggleston, 1925)); this fall of arterial pressure is often

that is unexplained until he asks to pass his water, after which act the arterial pressure returns to its previous level. Volhard (1931) has drawn attention to the raised arterial pressure shown by many subjects with retention of urine due to prostatic enlargement and urethral stricture, and to the fall of arterial pressure that follows drainage of the bladder. This observation I have confirmed several times.

The vascular reflexes from bladder distension have been extensively studied by Guttman and Whitteridge (1947) in patients with complete transection of the spinal cord, but in whom the cord below the lesion was intact. As Fig. 3.1 shows, in patients with transections below T₆, the rises of arterial pressure produced by distending the bladder were small, of the order of 10 to 20 mm. Hg. In these patients bladder distension produced conspicuous vasoconstriction in the toes, but vasodilatation in the fingers and flushing of the skin of the face, neck and upper chest. In patients with higher transections, distension of the bladder produced enormous rises of arterial pressure, for example, from 100 mm. Hg systolic to 250 mm. Hg, with vasoconstriction in both fingers and toes. The explanation of these very striking differences is not by any means certain. The sympathetic supply to the upper limbs leaves the cord between the 3rd and the 7th or 8th thoracic roots. It would seem that bladder distension produces a fairly generalized vasoconstriction reflexly through the spinal cord. The rise of blood pressure excites a mechanism, presumably the baroreceptors of carotid sinus and aortic arch, and induces vasodilatation in that part of the body whose vessels are supplied with sympathetic fibres from the cord above the lesion. If the lesion is high enough, then there is too little available for compensatory dilatation and so the rise of pressure is enormous. These facts therefore suggest how extremely important these baroreceptors are in regulating arterial pressure. In the spinal cat, rises of arterial pressure have also been induced by distending other hollow viscera (for references see Guttman and Whitteridge, 1947).

EFFECT OF POSTURE

Many observers, starting with Erlanger and Hooker (1904), have shown that when the blood pressure is measured in an arm maintained at heart level, a change of posture from lying to sitting or from sitting to standing is accompanied by small and very variable changes in systolic and diastolic pressure. Usually, the change in diastolic is negligible, while systolic pressure and pulse rate tend to rise slightly with the assumption of the upright posture.

The effects of posture have recently been studied more fully by Brigden, Howarth and Sharpey-Schafer (1950), using a swing couch and measuring cardiac output by the Fick method and cardiac catheter-

vasoconstriction to balance reduced cardiac output, and partly by the onset of the vasovagal faint presently to be described (Brigden, Howarth and Sharpey-Schafer, 1950 ; Edholm, 1952).

THE FAINTING ATTACK

In certain subjects painful stimuli produce a very different response, which in its full form is the fainting attack or vasovagal attack of Lewis (1932). These attacks may be produced by pain arising from the skin (personal experience of two subjects), but are much commoner with pain of the deep somatic or visceral type. Cowell (1928) has described this type of response in renal colic. The attack may be provoked by sensations which have an association with injury such as the sight of blood. The fainting attack is common in those who have lost blood, as from a haematemesis, and occurred in 3.8 per cent. of blood donors who had lost 440 ml. of blood and in 8.5 per cent. of those who had lost 540 ml. (Poles and Boycott, 1942). The fainting attack is particularly prone to develop if the subject stands or is tilted into the erect position. It may be prevented or relieved by adoption of the head down position. Wallace and Sharpey-Schafer (1941) bled 27 subjects up to 1,150 ml. Sixteen showed a fall of blood pressure with syncope. The fall of blood pressure on sitting up was exaggerated in all of nine subjects. Of 13 subjects bled over 1 litre, four had a pronounced fall of blood pressure and bradycardia.

Cotton and Lewis (1918) showed that there are two components of the fainting attack, namely, slowing of the heart and fall of blood pressure. The slowing of the heart can be prevented by intravenous injection of 1/50 grain atropine and is therefore presumably vagal. The fall of blood pressure is not affected by atropine, and thus depends on a different mechanism. The nature of the fainting attack has been elucidated by the studies of Barcroft, Edholm, McMichael and Sharpey-Schafer (1944). These workers have generally induced fainting by venesection or trapping blood in the legs with cuffs inflated on the thighs, and then tilting to the erect posture. Cardiac output usually falls when blood is removed or trapped, but it may show no further fall during the faint, despite the slowing of the pulse and the profound fall of systolic and diastolic pressures. Blood flow through the forearm rises during the faint, while that through the liver and kidney is generally unchanged, despite the fall of arterial pressure (Bearn and others, 1951 ; de Wardener and McSwiney, 1951). Cerebral blood flow appears to be reduced (Lennox, Gibbs and Gibbs, 1935). Thus the basis of the faint appears to be a profound vasodilatation affecting muscle particularly and the splanchnic area to a less extent. The forearm vasodilatation is absent in the sympathectomized limb and is larger than can be accounted for by paralysis of sympathetic

accompanied by giddiness and sometimes by loss of consciousness. Stead and Ebert (1941), Jeffers and others (1941) and Verel (1951) have shown that the fall of blood pressure on standing is due to the failure of the compensatory vasoconstriction that occurs in normal subjects. The heart rate is often unchanged. Verel has shown that the vasoconstrictor responses to warming the body, and to taking a deep breath, are intact. The latter is known to be a spinal reflex (Gilliat and others, 1948), and the efferent path of both is known to be sympathetic (Lewis and Pickering, 1931; Bolton and others, 1936). On the other hand, there is no vasoconstrictor response to a cold or painful stimulus applied to the skin, the efferent path of which reflex is also sympathetic. It therefore seems that the lesion here lies in the central nervous system and that it results in the failure of the afferent impulses from the baro-receptors to make connection with the spinal efferent sympathetic mechanism (Verel 1951). From this standpoint it is of some interest that these patients do not usually have hypertension. Cases of postural hypotension have been described following encephalitis, syringomyelia, hæmatomyelia, tabes dorsalis, encephalomalacia and tumours. Hammarström and Lindgren (1942) in one case found lesions in the right internal capsule, cerebellum, occipital lobes and lateral parts of the cerebral hemispheres. Luft and v. Euler (1953) showed that in two cases, the urinary excretion of noradrenaline was diminished, and that there was no increase in the excretion of adrenaline as occurs in normal subjects in response to insulin hypoglycæmia or subcutaneous histamine, though infused noradrenaline was excreted normally. The defect thus also involves the central or peripheral mechanisms governing the secretion of adrenaline by the adrenal glands.

Standing still for long periods, particularly in hot weather, may produce a profound fall of arterial pressure and loss of consciousness, particularly if the skin vessels are dilated. A ceremonial parade of the Guards provides just these conditions, and much disgrace attaches to the unfortunate victim who, with a clatter of rifle and accoutrements, falls senseless to the ground. Fainting on standing is not uncommon in more ordinary members of the community, particularly adolescent girls and pregnant women. The mechanism behind the simple postural faint is complex. Krogh, Landis and Turner (1932) showed that with immobility of the body in the erect or nearly erect position, hæmoconcentration occurs, no doubt because of the large rise in capillary pressure and consequent transudation from the capillaries in the lower part of the body. This and the pooling of blood in the belly and legs may reduce the cardiac output to a level at which arterial pressure can only be maintained by severe and widespread vasoconstriction. Fainting appears to be induced partly by a failure of

ately after exercise and then fell to reach normal in under two minutes. This rise of pressure affected chiefly the systolic value, the diastolic being affected little. The rise of pressure was proportional both in degree and duration to the intensity of the exercise.

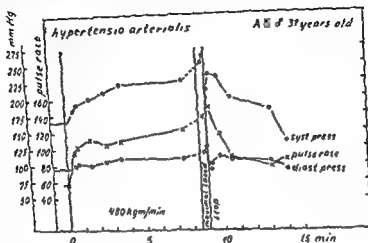


FIG. 3.4. Shows the effects of exercise on a subject with mild hypertension (Eskildsen and others (1950))

Eskildsen, Gotzsche and Hansen (1950) have investigated the effects of exercise performed upon a bicycle ergometer. Arterial pressure was measured directly with a condenser manometer. The results are illustrated in Figs 3.3 and 3.4. Systolic pressure and pulse rate rose during exercise and at low rates of exercise reached a plateau. When the rate of exercise was varied the rises of pulse rate and systolic blood pressure increased with increase in rate of exercise. The diastolic pressure was virtually unaltered until the highest rates, when it rose slightly. When exercise was stopped, the blood pressure might fall abruptly and then rise again, or it might fall gradually. Fig. 3.4 shows a record from a patient with hypertension, enlarged heart and eyeground changes

PSYCHOLOGICAL FACTORS

It is common knowledge amongst medical men that the arterial pressure is greatly influenced by the patient's state of mind. In clinical practice, the most familiar is apprehension or fear which raises pressure, as was noted by Fraser and Cowell (1919) who measured

emotion
method of inducing excitement and noted that the rise of arterial
O'Hare (1920) used conversation as a

vasoconstriction, and must be partly mediated through vasodilator nerves (Barcroft and Edholm, 1946). During the faint the subject sweats profusely, he salivates and he is nauseated and may be sick. His face becomes deathly pale and the secretion of urine falls, both these changes persisting for some hours after the faint. These latter changes are precisely those produced by posterior pituitary hormone, and in fact Taylor and Noble (1950) have observed an increase in the excretion of antidiuretic substance in the urine two hours after fainting. They estimate that up to 2-4 units of antidiuretic hormone may be secreted during a faint.

These two modes of response to sensory stimuli, diametrically opposite in their effects on arterial pressure, would seem to have very different functions. The pressor response would seem to be part of a process in which the subject becomes prepared for action; the respirations quicken, the palpebral fissures widen, the muscles tense, and the subject becomes more alert. The fainting response on the contrary would seem to be a device to protect against hæmorrhage, for the arterial pressure falls profoundly and the subject is immobilized by loss of consciousness.

EXERCISE

Most of the earlier observations on the effects of exercise were obtained by the indirect method and confined to observations before and after exercise (Cotton, Rapport and Lewis, 1917). These showed that immediately after the end of exercise arterial pressure was a little higher than before exercise, and that the pressure rose to reach a maximum after twenty to forty seconds, subsequently falling to its original level after some minutes. The pulse rate was fastest immedi-

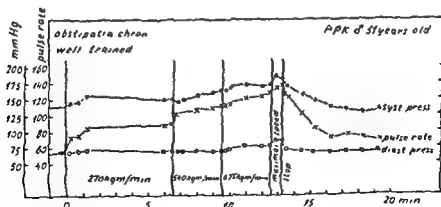


FIG. 33. Shows the effects of exercise at three rates on pulse rate and blood pressure of a normal subject. The arterial pressure was measured from an intra-arterial cannula connected to a capacitance manometer (Eskildsen, Gatzsche and A. T. Hansen (1950), *Acta med. scand., Suppl.* 239, 245).

measure. In Chapter 2 we have noted that the inflation of a sphygmomanometer cuff affects the systolic and diastolic values locally in the artery above it. Even more important are the effects on the general arterial pressure. All strong sensory stimuli increase arterial pressure, just as they tend to produce vasoconstriction in the skin. These sensory stimuli are, of course, strongest in the direct methods, involving arterial puncture, and for this reason alone, the indirect methods will retain their usefulness.

Even the indirect methods tend to raise arterial pressure, as was noted by Kapsammer in 1899. As the subject becomes more used to the procedure the blood pressure tends to fall. The blood pressure of 100 healthy medical students seated at a table was measured every five minutes for an hour by Diehl and Lees (1929). They found that the blood pressure fell significantly for the first three readings. After that the differences between successive readings were less than the probable error of the differences, until the eighth reading, which was the lowest, the pressure then gradually rising to the twelfth.

Ayman and Goldshine (1940) obtained readings in the home and in the clinic in 34 patients with essential hypertension over long periods. The home readings were made daily by the patient or a member of the family. The home readings were lower in all, the difference amounting to 20 mm or more in diastolic pressure in 24 per cent. of the patients.

Hamilton, Pickering, Roberts and Sowry (1954a) measured the arterial pressure in 180 out-patients, selected at random, on a second occasion under conditions closely similar to those of the first measurement. A fall of pressure was observed in 87, a rise in 60. Rises were observed chiefly in those with the lowest pressure on the first occasion, the largest falls being observed in those with the higher first readings.

CASUAL, BASAL AND SUPPLEMENTAL PRESSURE

It is evident that the arterial pressure is much influenced by environmental agencies and by the state of the patient's mind. In an attempt to obtain figures that were more characteristic of the subject, Addis (1922) measured the arterial pressure in the early morning, soon after the subject had awakened and before he got out of bed. He termed the measurements basal pressures and those taken during the more varied circumstances of the day casual pressures. In 76 normal young soldiers in barracks, the basal pressure averaged $99/71 \pm 11/9.7$, while the pressure measured in 300 of the same group of soldiers during the day averaged $128/78 \pm 17/11.1$. The Joint Committee of the American Heart Association and the Cardiac Society of Great Britain and Ireland in 1939 recommended that "in detailed researches or

pressure so produced was greater in patients with hypertension than in two control subjects with normal blood pressures. Landis and Gullette (1925) exposed 12 male, 12 female subjects and one boy to fifteen different situations as varied as reading a passage from the Bible, inspection of pornographic pictures, decapitating a live rat, and performing mental arithmetic, reinforced with electric shocks. They found that changes of 8–10 mm. Hg. within a minute were common and observed changes as large as 20 mm. in a minute. They found no sex differences and no pattern of reaction bearing a one to one correlation with the intensity of feeling as judged introspectively. Scott (1930) showed a film to 100 men, of whom 86 were between 21 and 25 years old. The three scenes, a nude dancing girl, flogging and the destruction of a city were supposed to arouse emotions of sex, anger and fear. The changes in systolic pressures for the three scenes were : maximum, 41, 18 and 16 mm. ; minimum, —7, —17 and —19 ; mean, 14.3, —0.1 and —1.9 mm. Hg. respectively. Clearly sexual emotion produced by far the greatest rise in blood pressure. Like Landis and Gullette, they observed no correlation between the degree of emotion as reported introspectively and the degree of change in systolic blood pressure.

It is extremely probable that these standardized procedures tend to underestimate the effects of emotion on arterial pressure.

The cardiovascular effects of stimuli acting through the medium of the mind have been extensively studied by H. G. Wolff (1953) and his colleagues, whose work will be further considered in Chapter 10.

OTHER FACTORS

Exposure to heat, as to a hot bath, or to hot air, tends to reduce blood pressure; exposure to cold, as in a cold bath or exposing the stripped subject to cold air, tends to raise arterial pressure. Exposure to high altitudes is without significant effect until anoxæmia develops, when the arterial pressure rises. Dietary effects will be considered in Chapter 10. The menstrual cycle is commonly without effect, but Vaux (1927) has found that a rise of pressure sometimes precedes menstruation. I had one patient, a girl of 15 with malignant hypertension associated with a congenital obstruction to one renal artery, who had attacks of headache, convulsions and coma, that coincided with her menstrual periods for five successive months (Pickering, 1934, Case 3).

THE EFFECT OF THE PROCEDURE ITSELF

One of the most tantalizing aspects of the study of arterial pressure is that the methods used for measurement affect the value we seek to

SUMMARY

In this chapter some of the factors affecting arterial pressure have been considered. The effects of these factors are considerable and would seem, in general, to be greater the higher the initial arterial pressure. Clearly, any given arterial pressure is a characteristic only of that individual at that moment of time. It is, unfortunately, true that the factors affecting arterial pressure are so numerous, and those affecting it through the mind so complex, that it is extremely difficult to define the conditions so exactly that repeatable results may be obtained. The nearest approach is to secure complete bodily and mental rest when the arterial pressure approximates to a minimum value for that individual, the so-called basal pressure. Determinations of basal pressures are, however, exacting in time and only suitable for research purposes. As ordinarily taken, the arterial pressure may be termed the casual pressure and shows considerable fluctuation from day to day and minute to minute.

blood pressure the use of a basal pressure might be considered, after preparation similar to that used for basal metabolism," i.e. "10-12 hours after the last meal of the previous night, and after resting half an hour in a warmed room."

Alam and Smirk (1943) made extensive investigations of casual and basal pressures in normal subjects, both European and Egyptian, and in Egypt and the United Kingdom; also in patients with essential and renal hypertension. To determine basal pressure they used the method of emotional desensitization, i.e. the subject had the whole procedure explained and he lay in a quiet darkened room, in which the observer sat with him without moving, recording pressures at about minute intervals from thirty to forty-five minutes, until the results showed no change. The lowest level of blood pressure maintained for three consecutive readings during the half-hour period was accepted as basal. They found lower basal pressures in Egyptians than in Europeans in Egypt, and lower pressures for Europeans in Egypt than in the United Kingdom. They termed the difference between basal and casual pressure the supplemental pressure, and found that this was higher in essential than in renal hypertension. Finally, Smirk (1944) showed that a combination of the methods advocated by the Joint Report of the Cardiac Society of Great Britain and the American Heart Association (1939) and by Alam and Smirk (1943) gave lower values than either separately. Thus in 13 normal subjects, the casual blood pressure averaged 124.8/75.5, the basal pressure by the method of the Joint Committee averaged 117.7/73.4, by the method of Alam and Smirk 114.2/71.8, and by the combined method 108.5/69.9. Smirk also demonstrated that the supplemental and basal pressures were independent variables, and thus that the casual pressure was composed of two independent parts. Other workers have used hypnotic drugs in order to quieten the patient and to obtain basal pressures. The effects of hypnotics will be further discussed on p. 150.

Kilpatrick (1948), using the combined method of Smirk for measuring basal pressure, studied the variation of basal, casual and supplemental pressures in three groups of subjects: (1) normal subjects in whom casual diastolic blood pressure never exceeded 90 and no systolic pressure exceeded 140, (2) prehypertensive, in whom the arterial pressure was higher, but in whom the mean casual systolic pressure did not exceed 160, and the mean diastolic readings were all below 90, and (3) those with essential hypertension in which mean casual systolic pressures all exceeded 160 and whose mean diastolic pressures were all above 90. He showed that the daily casual fluctuations exceed the basal fluctuations in all groups, and that basal fluctuations were greatest in essential hypertension.

of ensuring that the amount of blood delivered every minute to the lungs and systemic circulation is adequate for the needs of capillary exchange in the organs. Thus we see the arterial pressure as a characteristic of the conditions of supply of blood to the capillaries where the essential function of the circulation is achieved. We may therefore consider some of the features of capillary exchange, and the relation of the arterial pressure to capillary pressure and flow in some of the organs of the body.

CAPILLARY EXCHANGE

The capillaries are tubes composed of a single layer of endothelial cells which are flat thin sheets when the capillaries are open but become thicker when the capillaries are shut. The changes in shape of these endothelial cells are probably responsible for the opening and shutting of the capillaries in response to chemical and nervous stimuli. The capillary loops in the human skin are 0.2 to 0.4 mm. long, and 0.02 mm. in diameter at the tip and venous end, narrower at the arterial end. Capillaries may be very numerous, averaging 2,630 per sq. mm. in the semimembranosus of the dog. In some organs, such as the human skin, they are ordinarily all open; in other organs, such as muscle, they are nearly all shut when the muscle is at rest, opening during exercise (Fig. 4. 2).

THE SUBJECT has been recently reviewed by Pappenheimer (1953). Lipoid soluble substances such as oxygen and carbon dioxide pass through the capillary wall extremely rapidly and it would seem that the whole extent of the cell membrane is permeable to them. Lipoid insoluble substances such as water and electrolytes are believed to pass between capillary and extracellular fluid through pores which may exist in the ground substance between the cells. It seems that even in the exchange of these lipoid insoluble substances diffusion is much more important than filtration and reabsorption. Thus it has been estimated that the rate of filtration, under "normal" conditions, of the perfused cat hindleg is 0.001 ml. per sec. per 100 g. tissue and half this value in the human forearm. The calculated rate of exchange of water by diffusion is 5 ml. per sec. per 100 g. muscle. So far as water is concerned the rate of exchange by diffusion is about 5,000 times that by filtration and reabsorption. The capillary wall itself appears to be freely permeable to small lipoid insoluble molecules but not to

CHAPTER 4

PHYSIOLOGICAL ASPECTS OF ARTERIAL PRESSURE

I. THE FUNCTIONAL IMPORTANCE OF THE ARTERIAL PRESSURE

ALTHOUGH, as we saw in the last chapter, the arterial pressure varies in response to the varying circumstances of everyday life, it is kept at some approximation to a constant level under given conditions ; and this is true also of most human subjects in whom the arterial pressure is high. Before we consider the factors affecting the arterial pressure and the mechanisms regulating it, we may consider the rather broader question of its functional importance. What is the value to a particular animal of having a certain arterial pressure and what would be the consequences of a lower or a higher one ? For while it is nowadays unfashionable to consider that all natural phenomena have a purpose, they are related to one another, and it is a constant source of surprise to the biologist to find how many characteristics of animals and plants seem to have a value to their possessors. Without prejudging the issue as to whether or not a raised arterial pressure serves any useful purpose, it is at least worth considering what that purpose might be.

The chief function of the circulation is the preservation of the constancy of the *milieu intérieur*, on which depends the proper behaviour of the cells comprising the several organs of the body. This takes place in the capillaries where the tissue fluids come into equilibrium with the blood plasma. In the lungs oxygen is gained, carbon dioxide lost ; in the gut the simpler substances into which the food is broken down by digestion are absorbed ; in the kidney the elaborate processes of filtration, reabsorption and secretion that result in the formation of urine take place, and in all the tissues, the raw materials of metabolism are taken from the blood, the surplus of end-products carried away. All these depend in the first instance on the physical conditions under which blood is supplied to the capillaries from the arteries.

The capillaries are supplied with blood from the high pressure high velocity arteries, and the blood is received into the lower pressure low velocity system of veins ; but neither the arteries nor the veins serve any other function than conduits for the blood to and from the capillaries ; excepting of course that variations in the size of these conduits have a profound effect on cardiac output and peripheral resistance. Indeed, the heart itself has the comparatively simple task

finger may be too small to measure. When the body is hot, blood flow through the terminal phalanx of the finger may amount to 100 ml. per 100 ml. of tissue per min. (Wilkins, Doupe and Newman, 1938). Similarly, the blood flow through the human forearm at rest may be 1.5 ml. per 100 ml. per min. Immediately after exercise of the forearm it may have risen to 30 ml. per 100 ml. per min. (Grant, 1938). Again the cardiac output at rest may amount to 5 litres per min. and in a trained athlete after severe exercise to 37.5 litres per min. (Hill, 1926). That such enormous changes can be made both in local flow, and in the circulation in its wider sense, and at the same time that the needs of the individual tissues can be safeguarded, is one of the most challenging facts of the circulation. It is against this background that the function of arterial pressure may be viewed.

The conditions of flow in a simple rigid tube are given by Poiseuille's equation which is discussed on p. 47. Blood vessels are, however, not rigid and have very complex branchings. It is not surprising therefore that Poiseuille's equation does not hold in detail (Landis, 1933). Nevertheless, Poiseuille's equation does indicate the relative importance of pressure viscosity, length and cross-sectional area in determining the rate of flow through the vessels.

The conditions of the circulation are complicated by the variations in total cross-sectional area of the vessels at different points in the vascular tree. This is shown in Table 4.1, modified from Mall (1888) for

TABLE 4.1. From Winton and Bayliss, 1948. Data from Mall, 1888.

Blood vessels	Number	Radius cms	Total cross- section sq cms	Velocity of blood cms / sec	Length cms.	Fall in pressure mm Hg	Fall in pressure per cm length
Mesenteric artery	1	0.15	0.07	168	6.0	0.8	0.15
Main branches of mesen- teric artery	15	0.05	0.12	101	4.5	3.2	0.73
Final branches of mesen- teric artery	45	0.03	0.13	83	3.0	7.7	1.98
Intestinal arteries	1900	0.0086	0.20	5.8	1.42	24.5	17.2
Final branches of intes- tinal arteries	26,600	0.0025	0.57	2.1	0.11	65	57
Branches to the villi	328,000	0.00155	2.48	0.48	0.15	4.0	29.5
Arteries of the villi	1,050,000	0.00112	4.18	0.29	0.20	5.2	26.0
Capillaries of the villi	47,360,000	0.00040	23.78	0.04	0.04	1.2	20
					Total	57.0	
Veins of the villi							
Veins between the villi and the submucosa	2,102,400	0.00132	11.59	0.1	0.10	0.7	7.0
Submucosal veins	137,400	0.00375	5.80	0.2	0.10	0.3	3.0
Final branches of intes- tinal veins	18,600	0.0064	2.32	0.5	0.15	0.4	2.7
Intestinal veins	26,800	0.0031	0.83	2.3	0.11	2.3	21.0
Final branches of mesen- teric vein	1,922	0.0138	0.84	1.4	1.43	3.5	1.0
Main branches of mesen- teric vein	45	0.073	0.79	1.51	3.81	0.2	0.05
Mesenteric vein	15	0.12	0.67	1.7	4.5	0.1	0.02
	1	0.3	0.28	4.2	6.0	0.05	0.01
					Total	5.55	

globulins (M.W. around 150,000); fibrinogen (M.W. 400,000) is present in traces only. The rate of diffusion of a substance in aqueous solution at a constant temperature is determined by the concentration gradient, by molecular size and by molecular shape and tendency to form aggregates of molecules. Thus small ions move faster than large; large molecules move more slowly and the relatively immense colloidal aggregates or micelles slowest of all. So far as the regulation of capillary exchange by diffusion is concerned, the number of open capillaries per unit area, their size, and the rate of blood flow are important. The more open capillaries per unit area, the more nearly will the concentrations of solutes in the tissues between the capillaries approach the concentration in the blood. The more rapid the blood flow, the nearer the concentration of solutes in the tissue fluids will approach that of arterial blood.

Filtration of fluid occurs from a capillary when the difference between the capillary pressure and the tissue pressure exceeds the difference between the colloid osmotic pressure of blood and tissue fluids. Since tissue pressure and tissue fluid colloid osmotic pressure are generally very small, the important components are capillary pressure and plasma colloid osmotic pressure. Landis (1934) has shown that in each species, frog, guinea-pig and man, pressure in the arteriolar end of the capillary tends to exceed, while at the venous end it lies below, the plasma colloid osmotic pressure. Thus ordinarily water and electrolytes are filtered out of the arterial end of the capillary and reabsorbed at the venous end. The amounts involved are, as we have seen, ordinarily small, and the small excess of filtration over reabsorption is removed as lymph. The importance of filtration and reabsorption is that a gross excess of one over the other may either overload the tissues with fluid causing oedema, or reduce the tissue fluid below that which is optimum for the metabolism of the cells (tissue dehydration). Thus the capillary pressure is important because on its relationship to plasma colloid osmotic pressure depends the regulation of the distribution of water in the body.

The function of the circulation may be said to be the supply of blood to the capillaries of the various organs at such a rate and at such a pressure as will enable them to preserve the amount and composition of the tissue fluid at the appropriate values both in rest and activity. We are a little apt to consider the circulation at its simplest, in the animal at rest. In fact the life of most mammals, not excluding man, is a highly varied one, calling for great changes in the blood flow to the different organs to match their varied activity, from complete quiescence to full activity. For example, in a human subject who is chilled and whose skin blood vessels are constricted by the nervous mechanisms regulating body temperature, the blood flow through the

arterial pressure seems to be one of the most important factors determining blood flow. In organs such as muscle where most of the arterioles and capillaries are normally closed, and the skin of the hand and foot,

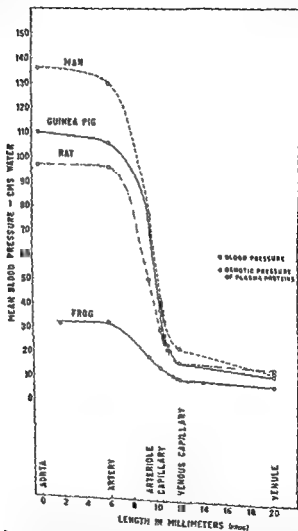


FIG. 4.1 Chart showing the fall of pressure (circles) in peripheral vessels of man, guinea-pig, rat and frog. Dots indicate the osmotic pressure of the plasma proteins (Landis, E. M. (1934), *Physiol. Rev.*, 14, 404).

where the chief conduits, the arteriovenous anastomoses, may be closed or open, blood flow is much less affected by arterial pressure than by the tone of the vessels. The regulation of vascular diameter is fully discussed in the third section of this chapter.

the intestinal vessels of the dog. The data given in this table show how the cross-sectional area rises to reach a maximum in the capillaries of the villi where it is more than 300 times as great as in the mesenteric artery, to decrease again, though to a lesser extent, on the venous side. These changes in cross-sectional area are, of course, matched by opposite changes in the velocity of blood flow, which is highest in the arteries and slowest in the capillaries where the actual exchange takes place. In detail, data given in this table are to be treated with reserve since they represent calculations made from the examination of dead material and it is doubtful whether the size of the individual vessels or the number of open capillaries during life is ever exactly the quantities given. Nevertheless the table does, in a general way, illustrate what happens to blood as it flows through the circulation from the arterial to the venous side.

THE RELATIONSHIP BETWEEN ARTERIAL PRESSURE AND CAPILLARY EXCHANGE

Fig. 4.1 shows the fall of mean pressure through the systemic vascular tree of guinea-pig, rat and frog. In each species the rate of fall of pressure is steepest in the small arteries, arterioles and capillaries, particularly in the arterioles, and relatively small elsewhere. In each species the capillary pressure equals the colloid osmotic pressure of plasma at about the mid-point of the capillary, being higher at the arterial, lower at the venous end. This represents the conditions in the organs at rest. During activity of the organ, when the local demand for blood is at its maximum, the vessels dilate. This dilatation, particularly of the small arteries and arterioles, diminishes the frictional resistance to the flow of blood, and so increases blood flow, at the same time raising pressure in the capillaries and beyond. It is probable that as a consequence capillary pressure exceeds the colloid osmotic pressure of the plasma throughout the length of the capillary, thus leading to an increase in filtration of tissue fluid, to a great increase in the flow of lymph and to temporary local œdema. In many organs such as muscle (Fig. 4.2), activity is accompanied by opening up of capillaries previously closed, thus spreading more widely the increased flow delivered by the arterioles.

The conditions of capillary exchange, that is to say, rate of blood flow and capillary pressure, can be regulated by two kinds of change, namely a change in the general arterial pressure, and a change in vascular diameter of the organ in question. The importance of these two mechanisms varies considerably for different tissues. Thus in the brain and heart, where perhaps the most vessels are persistently open,

arterial pressure seems to be one of the most important factors determining blood flow. In organs such as muscle where most of the arterioles and capillaries are normally closed, and the skin of the hand and foot,

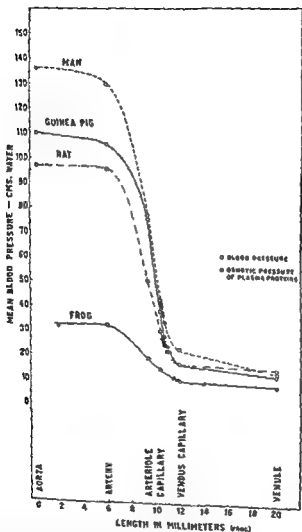


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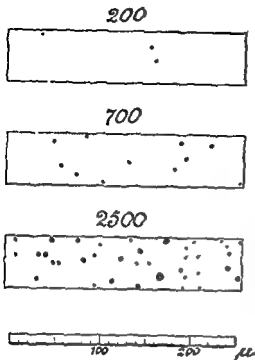


FIG. 4.2. Equal optical sections from three different muscles with the number of capillaries per sq. mm. as noted. The approximate diameters of the open capillaries are also indicated; in the working muscle they vary considerably while in the resting muscle with 200 open capillaries they are extremely narrow. The upper muscle is at rest, the lowest after exercise (Krogh, A. (1929), "The Anatomy and Physiology of Capillaries," 2nd Edition. New Haven: Yale University Press, p. 64).

COMMENT

A high arterial pressure implies increased cardiac work, and in man carries other disadvantages to be considered later. What can its advantages be? In the first place, it probably enables the animal quickly to raise the blood flow to an active organ through local vasodilatation. Animals with a higher pressure may therefore have a wider range of organ activity than those with lower pressures. In the second place, if the plasma proteins are increased in amount, a higher arterial pressure may be necessary to preserve the most suitable conditions for fluid exchange in the tissues. Thirdly, if there is any interference with the circulation to a particular organ, especially such an indispensable organ as brain, heart or kidney, a higher arterial pressure may be necessary to preserve the correct conditions of capillary exchange in that organ.

The reader may conclude, justifiably, that this discussion smacks of that highly dangerous philosophy, teleology. Nevertheless, the writer feels justified in presenting it, because it may suggest considerations that have been overlooked and which may lead to lines of work that may throw light on much that now remains obscure.

II. THE REGULATION OF THE ARTERIAL PRESSURE

Arterial pressure has a maximum or systolic, a minimum or diastolic and a mean value for each beat of the heart. In relationship to the

other physical values, it is the mean, rather than the systolic or diastolic arterial pressure that is generally considered. The mean value is an abstraction, since the pressure in the arteries is always pulsatile; nevertheless, the blood flow in an isolated organ perfused at a constant pressure is approximately the same as when perfused at a pressure which oscillates about the same mean value, though, curiously enough, the pulse pressure seems to influence the rate of excretion of water and sodium by the kidney (Selkurt, 1951). As has been seen in Chapter 2, the mean pressure is practically never measured in man. It can be calculated from the systolic and diastolic pressures if the shape of the pulse wave is known. It is always nearer the diastolic than the systolic value.

FACTORS DETERMINING THE PULSE PRESSURE

The effect of reflected waves on these pressures at specific points of the arterial tree has been mentioned in Chapter 2. Here we consider the factors that determine their relationship in the aorta. Since the discharge from the left ventricle is intermittent and the flow of blood through the arteries continuous, it is clear that a considerable fraction of the systolic discharge from the left ventricle is accommodated by expansion of the aorta and its larger branches. The difference between the pressures thus represents in part the force necessary to distend the aorta sufficiently to accommodate left ventricular output. The stroke volume, and the rate of emptying of the left ventricle are thus one set of determinants. On the other side is the distensibility or elasticity of the aorta. The elasticity of tubular structures is determined by measuring the volume increase when the internal pressure is raised by a definite amount. The ratio pressure increase to volume

increase $\left(\frac{dp}{dv}\right)$ is termed the volume elasticity coefficient (E_v), which

varies inversely as elasticity, directly as rigidity.

A great deal of work has been done on the elastic properties of arteries in different states of contraction, and of the aorta at different ages. This work is reviewed by Tigerstedt (1921) and Wiggers (1923) where fuller information can be sought. In muscular arteries, the volume elasticity coefficient, or rigidity, tends to increase progressively as the internal pressure rises, when the artery is relaxed; the reverse is true if the artery is strongly contracted. In the aortas of young subjects the rigidity increases very little at all at the higher tensions. As the age of

elasticity coefficient to tension begin to curve upwards at progressively lower pressures, until in very old age they are almost straight from the start (Fig. 4. 3).

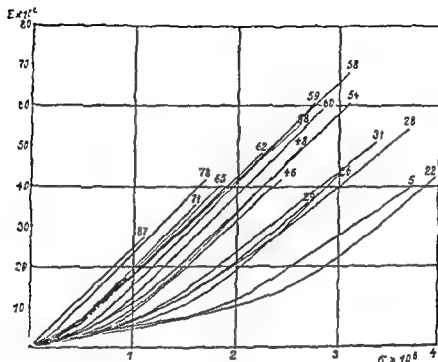


FIG. 4.3. Curves showing the elasticity coefficients E of aortas at different specific tensions (σ) at ages indicated on the chart. E and σ are expressed in 10^6 dynes, a unit which corresponds approximately to the pressure exerted by an atmosphere for cm^2 . The elasticity coefficient = $\frac{dp}{dv}$ v. The data were obtained by Frank (1927) with rings of aorta obtained *postmortem*. (Figure from Wiggers (1932), *Ann. intern. Med.*, 6, 12.)

From a practical point of view the pulse pressure is increased in the following clinical conditions :

(1) Conditions which increase the stroke volume of the left ventricle:

- (a) Bradycardia, e.g. complete heart block.
- (b) Aortic regurgitation.
- (c) Arteriovenous fistula.
- (d) Patent ductus arteriosus.
- (e) Severe anæmia.
- (f) Paget's disease of bone.
- (g) Thyrotoxicosis.
- (h) Fever.

(2) Conditions which increase the rigidity of the aorta and its larger branches :

- (a) Degenerative changes of the media as seen in old age, diabetes, etc.
- (b) Raised mean arterial pressure.
- (3) Decrease in the capacity of the aorta and its large branches :
coarctation of the aorta.

In all the above conditions except (2)(a) the underlying cause is obvious on thorough physical examination, and the increase in pulse pressure takes rather a subsidiary place. But in (2)(a) there may be no other physical signs. Since the increase in pulse pressure is chiefly effected through a rise of systolic pressure, this condition has been termed systolic hypertension. The increase in pulse pressure with age in the population at large is clearly shown in Fig. 8.1.

FACTORS DETERMINING MEAN ARTERIAL PRESSURE

The mean arterial pressure is determined by the relationship between cardiac output and peripheral resistance, as given by Frank's formula :

$$\text{Resistance (dynes cm.}^{-5} \text{ sec)} = \frac{\text{Mean pressure (mm. Hg)} \times 1,320}{\text{Cardiac output (ml. per sec.)}}$$

Peripheral resistance is in turn composed of the viscosity of the blood, and the length and cross-sectional area of the vessels forming the vascular tree. The relationship between these factors is expressed very approximately by Poiseuille's formula governing the rate of flow in rigid tubes

$$\text{Flow per sec.} = \frac{(P_1 - P_2)\pi r^4}{8\eta l}$$

where P_1 and P_2 are the pressures at the two ends of the tube,
 r is the radius of the tube,
 η is the viscosity of the fluid,
 l is the length of the tube.

Poiseuille's equation has limited application in the intact animal for the following reasons :

- (a) The tubes are elastic.
- (b) The cross-sectional area changes and the velocity changes at each subdivision of the vascular network (see Table 4.1)
- (c) The viscosity of blood is different according to the conditions under which it is measured (Whittaker and Winton, 1933)

Nevertheless, the equation does draw attention to the factors concerned and their order of magnitude.

The Cardiac Output

Methods of determining the Cardiac Output

Since no valid conclusions about peripheral resistance can be drawn without estimation of cardiac output, a few words must be said about methods. Unfortunately at the present time the only completely reliable method is that involving the Fick Principle and the use of cardiac catheterization, and this requires a formidable array of instruments, masked men and punctures which are not without their effects on the circulation of the conscious man. The only method that does not itself introduce profound effects on the circulation is the

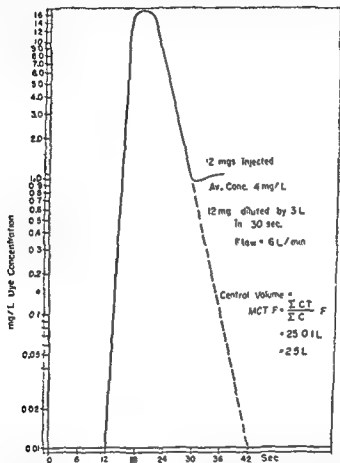


FIG. 4.4. Concentration curve in arterial blood resulting from the injection of dye, the dye concentration being plotted

ballistocardiograph, but unfortunately there is no convincing evidence that such estimates are entirely reliable. The chief methods available are briefly as follows :

(1) *The Fick Principle using Oxygen Consumption and Cardiac Catheterization.* This depends on the equation :

$$\text{Cardiac output (ml. per min.)} = \frac{\text{Oxygen consumption (ml. per min.)} \times 100}{\text{Arteriovenous oxygen difference (ml. per 100 ml.)}$$

The oxygen consumption must be determined during the experimental period, either by use of a Douglas bag or a spirometer of the Benedict-Roth type. Arterial oxygen content is measured in blood obtained by a Courmand needle inserted into the brachial or femoral artery, venous oxygen content in blood obtained by a catheter inserted into right auricle or, preferably, into right ventricle or pulmonary artery. If the cardiac output is changing during the experimental period, the arterial and venous samples should be smoothly withdrawn throughout the period. This method has been in use for many years, its chief limitation being the difficulty of obtaining mixed venous blood. Cardiac catheterization has solved this problem.

concentration becomes a straight line (Fig. 4.4). Calculation of mean arterial pressure

The method is good agree method is c (1931) hav followed by

(3) The ballistocardiograph records the movement with the heart beat of a subject lying on a freely suspended table. While it may be a useful empirical method it probably does not accurately reflect cardiac output (Starr and others, 1930; Cathcart and others, 1953).

Regulation of Cardiac Output

Patterson, Piper and Starling (1914) showed that in the dog's heart-lung preparation when the venous inflow was kept constant, a rise in arterial pressure produced an immediate decline in stroke output of the ventricles, but that the stroke output returned to its previous level as the diastolic size of the heart increased, increased cardiac work was accomplished through increased diastolic size effected by increased filling pressure. In human hypertension, the venous pressure is usually normal, probably because the abnormality has long been present and has been accompanied by cardiac hypertrophy. When, however, hypertension is induced acutely as by infusion of hypertensin (Wilkins and Duncan, 1941) or has happened recently as in acute nephritis, the venous pressure may be raised (Davies, 1951). An acute rise of arterial pressure has its chief effects however on the left

heart, and may result in acute pulmonary cedema, presumably due to a rise in left auricular pressure.

In the dog's heart-lung preparation, when arterial pressure is kept constant, cardiac output is determined chiefly by the venous inflow and by the venous pressure distending the heart in diastole. Fig. 4.5 shows the relationship between cardiac output and venous pressure under the circumstances. It will be observed that at low venous pressures and low outputs a small increase in venous pressure produces

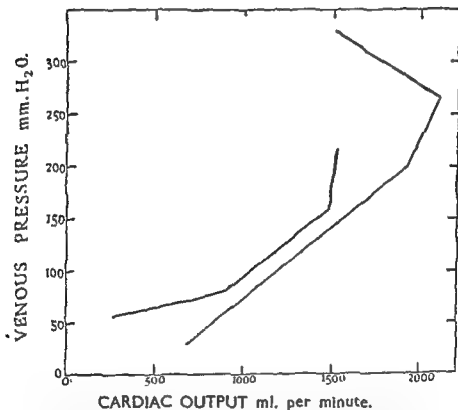


FIG. 4.5. The relationship between venous pressure and cardiac output in the isolated denervated heart-lung preparation (After Patterson, S. W., Piper, H. and Starling, E. H (1914), *J. Physiol.*, 48, 465).

■ relatively large increase in output. As venous pressure rises the effect on output gradually lessens, becomes zero, and finally a rise in venous pressure produces a fall in output. It is at present by no means clear to what extent the intact human heart behaves similarly. On general grounds, it would be expected to do so, with the important qualification that its behaviour may be profoundly modified by nervous and hormonal influences. The early observations of McMichael and

Sharpey-Schafer (1944) suggested that the behaviour depicted in Fig 4.6 was followed closely; in the normal heart, small changes in venous pressure induced by venesection or transfusion produced corresponding and large variations in output; in the failing heart, a reduction of venous pressure by venesection would increase the cardiac output. Subsequent observations with improved methods have, however, failed to confirm these observations in detail, although in a given subject in a given experiment, there is a striking relationship between the end diastolic pressure in the right ventricle and the pressure developed in the next systole (Lauson and others, 1946). Hamilton (1953) takes the view that the nervous and hormonal influences acting on the intact heart protect it against being exposed to the degree of strain which finds expression in Starling's law. For a given venous pressure, adrenaline appears to increase cardiac output as does stimulation of the cardiac sympathetic nerves, while stimulation of the vagus tends to lower it. The importance of hormonal and nervous influences is demonstrated by the remarkable radiological observations of Liljestrand and others (1939) that during exercise in man, despite the rise of cardiac output and arterial pressure, the diastolic volume of the heart may actually fall.

It would be expected that a rise in arterial pressure would reduce cardiac output and, from Poiseuille's formula, that a rise in cardiac output would increase arterial pressure. We have noted the compensatory devices in the heart itself which oppose the first effect. The second effect is opposed chiefly by the homeostatic reflexes which adjust the peripheral resistance, and which will be discussed later in this chapter.

The venous inflow on which the cardiac output is so closely dependent, is determined by the relationship between the blood volume and the capacity of the circulation, and the pumping action of muscular movements on venous flow from the extremities, and of respiratory movements of the thorax and abdomen on venous flow in abdomen and thorax (for a full account of which reference should be made to a current textbook of physiology). The capacity of the circulation is apparently capable of considerable adjustment. Thus in severe anaemia, the total blood volume may be much reduced, while the cardiac output is doubled (McMichael and others, 1943). Conversely, in polycythaemia the blood volume may be increased while the cardiac output is normal.

This discussion on cardiac output illustrates with great clarity the difficulty of considering any single characteristic of the circulation except in relationship to the circulation as a whole and with the proviso, which is very rarely satisfied, that all other factors remain unaltered. The frustrated investigator all too often finds that his argu-

ments closely imitate the behaviour of the blood in following a circular course. For this reason alone the consideration of the remaining physical factors on which arterial pressure depends will be made very brief.

The Viscosity of the Blood

The viscosity of the blood is largely dependent on its corpuscular content. Viscosity also greatly depends on the conditions of flow, being very different in the slow velocity viscometer of Ostwald, a high velocity viscometer and the isolated hind limb (Whittaker and Winton, 1933). As we shall see, the very high viscosities of polycythæmia may be accompanied by no elevation of arterial pressure, and conversely the very high pressures of the terminal state of nephritis may be associated with the very low viscosities of severe anæmia.

The Peripheral Resistance

The peripheral resistance is composed of two components, vascular length and vascular cross-section. Each of these may be measured with the microscope in transparent or superficial tissues or on the surfaces of organs after exposure. In practice, however, resistance is deduced from the measurements of pressure and of flow. Changes in resistance can be safely attributed to changes in vascular radius, which from Poiseuille's equation acts to the fourth power in influencing rates of flow. Differences in resistance between individuals are also usually attributed to differences in vascular radius, but may equally well be due to differences in vascular length, a factor which is generally overlooked in contemporary discussion.

PROPRIOCEPTIVE VASCULAR REFLEXES. REFLEXES FROM THE BARO-RECEPTORS

The constancy of the arterial pressure and of the other characteristics of the circulation would seem to be due at least in part to proprioceptive reflexes from the vascular system. Pre-eminent amongst these are the carotid sinus and depressor reflexes so beautifully displayed by Hering (1927) and by Heymans and their pupils. There is a good deal of evidence, summarized by Dawes (1952) suggesting that baro-receptors are also present in the great veins and auricles on both sides of the heart, and possibly in the pulmonary arteries and their branches and in the left ventricle. Impulses, synchronous with the heart beat and whose frequency is increased by raising the pressure

in the mesenteric artery have also been recorded from the splanchnic nerves. They are thought to arise from the Paccinian corpuscles of the mesentery. Except in the case of the carotid sinus and depressor nerves, very little is known of the effects of stimulating these receptors or of the part they play in the regulation of the circulation, but what evidence there is suggests that they may all behave similarly in pro-

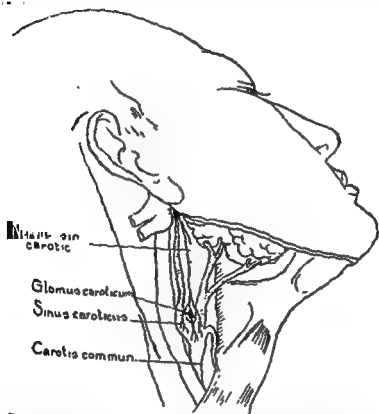


FIG. 4.8. A drawing of the carotid sinus, the carotid body (glomus caroticum) and the carotid sinus nerve in man (Heymans, C. (1939), *Irish J. med. Sci.*, 717)

ducing effects on the heart through the vagus and on the vessels through the sympathetic nerves.

The importance of chemo-receptors in the vascular system is also becoming recognized. The best known is the carotid body which is particularly affected by oxygen lack, and by CO₂ tension and effects on the

circulatory and pulmonary circulations.

Stimulation of these receptors which is the basis of the action of veratrine (see p. 323) produces reflex slowing of the heart and a fall of arterial pressure with vasodilatation in the intestines and lower extremities (Bezold reflex) and slowing of respiration. It is, of course, tempting to suggest that the cardiac slowing, fall of arterial pressure and vomiting of myocardial infarction similarly arise from these chemo-receptors in the heart.

The Carotid Sinus and Depressor Reflexes

Although the existence of the depressor nerve was known before, the understanding of these reflexes begins with Hering in 1927. Czermak (1879) had shown in 1868 that compression of the region of the vagus nerve in the neck produced slowing of the heart, and this procedure was in regular use for interrupting attacks of paroxysmal tachycardia. Hering doubted the current explanation, considering that the pressure employed was quite insufficient to stimulate nerve fibres. Exposing the tissues of the neck, he showed that the sensitive region was the expansion on the origin of the internal carotid artery (the carotid sinus, see Fig. 4.6), and that when this was denervated by clearing away all tissue lying between it and the internal carotid, this sensitivity went. The researches of Hering and his school, Heymans, Bouckaert and Regniers (1933) and of numerous other workers, have shown the importance of the role of baro-receptors lying in the aortic arch and carotid sinus in the reflex regulation of blood pressure. The nerve endings in the wall of the artery are illustrated in Fig. 4.7. They are distributed in a lamellar fashion between the coats of the artery.

Electrical recording has shown that a burst of impulses ascends the carotid sinus and depressor nerves at each heart beat. The frequency of impulses is increased when arterial pressure is raised, decreased when it is lowered. Stimulation of the sinus nerve or the depressor nerve causes reflex slowing of the heart and reflex vasodilatation which is more or less generalized, involving, for example, the skin, muscles, intestine and spleen. Raising the pressure in the carotid sinus (Figs. 4.8 and 4.9) or aortic arch has the same effect. Section of the nerves or lowering the pressure in the carotid sinus after the aortic depressor nerves have been cut causes quickening of the heart, largely by an inhibition of vagal but partly by a reduction in sympathetic tone, vasoconstriction in the territories mentioned and a release of adrenaline from the adrenal gland. The extent of vasoconstriction in any territory is influenced by the degree of activity of the tissues, and hence its demands for blood. Thus the muscle vessels ordinarily respond, but when dilated after exercise, they escape. The cerebral circulation is the one territory in the body which seems to be unaffected in these

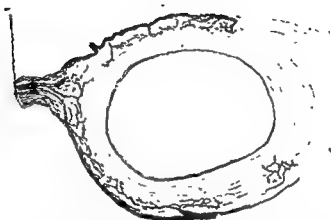


FIG 47 Nerve endings in the carotid sinus (preparation by Dr. Estable, Montevideo)

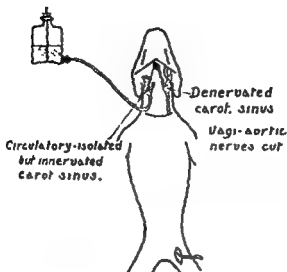


FIG 4.8. Technique of establishing the circulatory isolated but innervated carotid sinus in the dog (Heymans, C. (1939), *Irish J. med. Sci.*, 717).



FIG. 4.9 shows the effect on blood pressure SBP and respiration R, of changing the pressure in the isolated innervated carotid sinus (CBP) prepared as depicted in Fig 4.8. Time in min. At 1 and 3 raising the pressure inside the sinus induces reflex inhibition of respiration and decrease of systolic blood pressure. At 2 and 4 reducing the pressure in the sinus induces the reverse changes in respiration and circulation (Heymans, C. (1939), *Irish J. med Sci*, 717).



reflexes (Bouckaert and Heymans, 1935) ; and if a teleological attitude is adopted, it might be said that the function of these reflexes is primarily to adjust the circulation so that the arterial pressure is adequate to maintain unaltered the cerebral circulation.

These reflexes are thus perfectly designed for the reflex control of arterial pressure in that the receptor organs respond accurately and quickly to changes in arterial pressure, exciting reflexly cardiovascular effects that oppose the change. It will not escape notice that, as Hering pointed out, the receptors are placed on the approaches to the two master organs of the body, the brain and heart, whose intimate dependence on oxygen for their function, and on arterial pressure for their supply of oxygen, is outstanding. That they play a most important part is shown by the following experiments :

(1) If, in a dog, with aortic nerves sectioned, the arterial pressure is kept constant by perfusion of an isolated carotid sinus, the pressor effect of adrenaline and the depressor effect of acetylcholine are greatly increased by denervating the other carotid sinus (Cuypers, 1935).

(2) The fall of blood pressure, provoked by section of the splanchnic nerves, and the rise of blood pressure provoked by splanchnic stimulation, are enhanced by section of the carotid sinus nerves.

(3) After section of the carotid sinus nerves and depressor nerves, the animal is much less resistant to hæmorrhage, trauma and spinal anæsthesia (Heymans, Bouckaert and Regniers, 1933). These observations not only demonstrate the importance of the reflexes in the control of arterial pressure, but also in protecting the body against incidents which may disturb the circulation.

It had always been assumed that these reflexes were aroused by simple stretching of the arterial wall and Volhard (1948) therefore suggested that hypertension might be due to an increase in tone of the arterial wall, and therefore a decreased distensibility of the baroreceptors and decreased impulse frequency in their nerves. Observations by Heymans and Van den Heuvel-Heymans (1950), Landgren, Neil and Zotterman (1952) and Heymans (1952) have shown that local application to the carotid sinus of drugs which alter the tone of the arterial wall does alter the activity of the reflexes, but in the opposite sense. Substances such as adrenaline and noradrenaline which increase arterial tone, increase the stimulation of the nerve endings and decrease arterial pressure and pulse rate. Conversely, substances such as priscol, papaverine, potassium chloride or sodium nitrate, which decrease arterial tone, decrease the stimulation of the nerve endings and therefore increase arterial pressure and pulse rate. Heymans (1952) has suggested that some such disturbance may be at the root of hypertension, but the same objections apply to this as to other hypotheses concerning disturbances of these reflexes being the primary cause of hypertension.

Section of the carotid sinus and depressor nerves produces a rise of blood pressure and heart rate, particularly when the animal is subjected to stimuli which tend to raise pressure. Because these nerves are essentially depressor they have been termed "Blutdruck-zügler," moderator and buffer nerves.

Since the activity of these reflexes is so intimately affected by every change in general arterial pressure, the state of these reflexes in hypertension, both in man and in the experimental animal, is a matter of great importance. Unfortunately the methods of testing this activity are extremely crude. In the intact animal, the measurement of the effects on blood pressure and pulse rate of occluding one or both carotid arteries, and the effect of digital pressure on the sinus, are about the only methods available. This question will be referred to again on p. 145.

While these are the chief vascular proprioceptive reflexes, they are not the only ones. Heymans (1929) showed by cross circulation experiments that even after section of all four nerves, bleeding induces reflex vascular changes.

The importance of these proprioceptive reflexes has been illustrated in Chapter 3 by the reflex adjustments to change in posture, which in intact man are so delicate that the arterial pressure at the level of the root of the neck scarcely alters when the subject is swung from horizontal to vertical. Another example is the maintenance of the arterial pressure when the blood volume is reduced by amounts of the order of 20 per cent by bleeding, despite the considerable changes in cardiac output.

OTHER VASCULAR REFLEXES

Although other vascular reflexes are not strictly relevant to the control of arterial pressure, they are worth mentioning here because so much misleading work has been done on this subject through lack of familiarity with elementary physiology. All strong sensory stimuli applied to the organs of special sense, an unpleasant smell, noise, a touch, etc.,

as is the case with the vagus nerves. Some deep sensory stimuli, e.g. renal colic, pain of the "sickening" type, tend to produce the fainting attack called by Lewis (1932) the vaso-vagal syndrome, because its effects resembled the effects on the vessels and the vagal effects on the heart induced by stimulating the carotid sinns and depressor nerves.

Cold applied to any part of the integument produces cutaneous vasoconstriction by two mechanisms, reflexly through sensory nerves in the skin, and centrally through action of a central receptor excited by the cooled blood (Pickering, 1932). Heat produces dilatation by

two similar mechanisms but the cutaneous reflex has the unexpected property of being mediated through the sympathetic nerves as afferent nerves (Cooper and Kerslake, 1953). Thus skin blood flow at any point of time is chiefly dependent on the summation of the effects on these various receptors subserving body temperature regulation. Thus, under the usual environmental conditions, skin blood flow is, to a considerable extent, determined by the state of thermal equilibrium of the body, and does not necessarily reflect the state of the circulation elsewhere.

III. THE REGULATION OF VASCULAR TONE AND TISSUE BLOOD FLOW

In the last chapter it was pointed out that the control both of the total cardiac output and of the share of it delivered to the individual organs is largely effected by alterations in vascular size. Since the peripheral resistance is an expression of vascular tone, it will be clear that the arterial pressure itself is thus also largely an expression of the state of the blood vessels in the body as a whole. In this section the mechanisms regulating vascular tone will be considered in greater detail. It would seem that the general needs of the organism are catered for by the reflexes, of which the sympathetic-adrenal system is the chief agent, and perhaps by the renin-hypertensin system. The local demands for blood are probably largely effected through the release in the organ concerned of vasodilator substances. These several agents will now be considered.

THE NERVOUS AND CHEMICAL CONTROL OF THE BLOOD VESSELS

1. The Sympathetic-adrenal System

Anatomically and functionally the sympathetic nerves and the medulla of the suprarenal gland are so closely related that they should be considered together.

Anatomy

The sympathetic nerves arise from small cells located in the lateral horns of the spinal cord from the first thoracic to the second or third lumbar segments. The medullated axons from these cells leave the spinal cord by the anterior spinal roots from the first thoracic to the second or third lumbar segments as the white rami communicantes. These so-called preganglionic fibres then pass to the paravertebral sympathetic ganglia, some twenty in number on each side. In these ganglia some of the preganglionic fibres terminate in dendrites, which are in contact with motor cells whose axons are non-medullated and form the postganglionic fibres. These postganglionic fibres pass as

bundles, the grey rami communicantes, to the spinal nerves by which they are distributed to the vessels, sweat-glands and pilomotor mechanisms of the trunk and limbs.

The supply to the head and neck and viscera is modified. Preganglionic fibres from the first to the fifth thoracic segments run through the relevant paravertebral ganglia and pass up the neck as the cervical sympathetic trunk; these fibres terminate in either the inferior, middle or superior cervical ganglia, whence postganglionic fibres pass to the structures of the head and neck, and via the cardiac nerves to the heart and lungs. Preganglionic fibres from the last seven thoracic roots pass through the ganglia and are collected into three bundles, the greater, lesser and least splanchnic nerves, which end in the coeliac and adjacent ganglia in front of the abdominal aorta, whence postganglionic fibres are distributed to the upper abdominal viscera. Fibres from the lower thoracic and upper three or four lumbar nerves pass through the ganglia of the lumbar sympathetic trunk to the inferior mesenteric ganglion, from which postganglionic fibres are conveyed through the hypogastric and pelvic plexuses to the pelvic viscera. The sympathetic fibres to the adrenals are preganglionic medullated fibres. The chromaffin cells of the medulla thus are homologous with ganglion cells and their postganglionic axons.

Most of the sympathetic fibres supplying skin and voluntary muscle reach their destination via the mixed nerves; there are other fibres forming a plexus around the large arteries, but most of these do not reach the smaller divisions of the arteries of the limbs and parietes of head and trunk.

From the function of

... .. pass through the vasomotor centre of the medulla, but in certain of the reflexes the pathway is spinal, notably those excited by a deep breath and from a full bladder (see pp. 30 and 27). The axon reflex was first described in postganglionic sympathetic fibres. No reflexes are known in which the preganglionic and postganglionic fibres are involved without the path involving the central nervous system, that is to say, the sympathetic ganglia are not reflex centres, but rather relay systems through which a single preganglionic fibre can actuate several nerve cells and their postganglionic fibres. Recently Boyd and Munro (1949) investigated the retention of an area of sweating in the dermatomes T₁₂ to L₃ after paravertebral ganglionectomy in man. They attribute this to the presence of intermediate ganglia situated deeply between the spinal roots and the paravertebral ganglia. Similar ganglia are also

two similar mechanisms but the cutaneous reflex has the unexpected property of being mediated through the sympathetic nerves as afferent nerves (Cooper and Kerslake, 1953). Thus skin blood flow at any point of time is chiefly dependent on the summation of the effects on these various receptors subserving body temperature regulation. Thus, under the usual environmental conditions, skin blood flow is, to a considerable extent, determined by the state of thermal equilibrium of the body, and does not necessarily reflect the state of the circulation elsewhere.

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Vasodilator fibres have also been demonstrated in the case of skin and muscle and may supply other organs. All orders of vessel, with the possible exception of the aorta and its largest branches, are affected by sympathetic activity. Unquestionable effects have been obtained on arteries, arterioles, capillaries, veins and arteriovenous anastomoses.

Cutting the sympathetic or temporarily interrupting it by local anaesthesia increases the blood flow through most tissues, other than brain and kidney, which are unaffected; the coronary flow may perhaps be diminished, but no measurements are known to the writer.

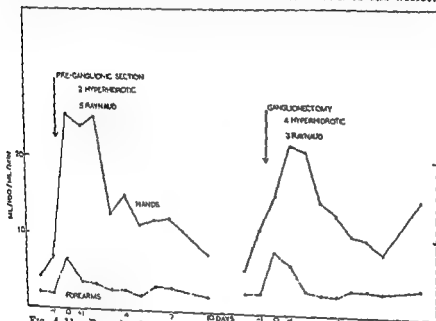


FIG. 4.11. Records of the effect of sympathectomy on the blood flow in the forearm and hand. The curves show the blood flow in the forearm (top) and hand (bottom) in a subject who had been treated with hypertensive drugs (Rainwater, 1935).

The blood flow does not remain at its maximum value long; after twenty-four or forty-eight hours it begins to fall, and after ten or fourteen days reaches a value that is, in many organs, no greater than before section (Fig. 4.11). Regain of tone parallels an increased reactivity of the vessels to adrenaline and other substances such as pituitrin, histamine and ergotoxin (Grant, 1935). This regain of tone and increase in reactivity after denervation are common to most structures investigated, and the mechanism of these very striking changes has aroused much discussion (Cannon and Rosenblueth, 1919; and Burn, 1953). Some think that the phenomenon is due to disappearance from the denervated motor unit of the enzyme systems

found in the cervical and lower lumbar regions. These intermediate ganglia do not appear to supply viscera. There is also suggestive, but far from conclusive, evidence for ganglion cells in relation to the peripheral blood vessels (Burn, 1953). Nevertheless, there is little doubt that the major part of sympathetic activity is interrupted by excision of the relevant paravertebral ganglia.

The Effects of Stimulating and Excising Sympathetic Nerves

The sympathetic nerves supply the blood vessels of all organs. Stimulation of the sympathetic usually produces vasoconstriction, except in the heart, where vasodilatation occurs, but the intensity of the effect varies from one organ to another, being, for example, very slight on the cerebral vessels and very great on the skin (Fig. 4.10).

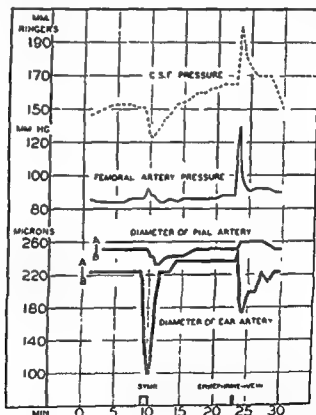


FIG. 4.10. Shows the cerebrospinal fluid pressure, the femoral artery pressure, and the diameter of pial and ear arteries of a cat. The diameter of the pial artery decreased 56 per cent. in the pial artery and 56 per cent. in the ear artery. 1 ml. of

ganglionic section (Freeman and others, 1931), and the latter operation has been performed in man in the hope that subsequent regain of tone will be less. Measurements of blood flow through the hand have, however, shown very little difference in this respect between the two operations in man (Fig. 4.12) (Walker, Lynn and Barcroft, 1950).

When large territories are denervated the arterial pressure falls abruptly and then slowly rises to near its original value. Even after total extirpation of the thoracic and abdominal chains and their associated paravertebral ganglia, the arterial pressure eventually recovers to a value not far below that before operation, in the cat and the dog. The totally sympathectomized cat is a miserable creature, that sits immobile in its cage and is very susceptible to cold. The dog, however, as Bacq, Brouha and Heymans (1934) have shown, is very different. After complete ganglionectomy the dog has not only a normal arterial pressure, but its capacity for work, as illustrated by a dog fight or running, seems unimpaired.

How the stimulation of the sympathetic nerves is

In the case of the dog, stimulation of the sympathetic nerves has been shown to produce a rise of arterial pressure (Bacq, Brouha and Heymans, 1934), but stimulation of sensory nerves produces not a rise but a fall. Brown and Maycock (1940) have shown that in the decerebrate animal this fall is abolished by curare and is due to the vasodilatation associated with muscular movement.

The Vasomotor Reflexes and the Vasomotor Centre

In the last section the homeostatic vasomotor reflexes arising from the baro-receptors in the carotid sinus, aortic arch and other regions and the reflexes controlling body temperature, were discussed. The sympathetic nerves and the adrenal glands form the chief efferent paths of these reflexes. These reflexes are not, however, the sole originators of sympathetic activity, to a large extent they control or modify it. Thus when the arch of aorta and carotid sinus are denervated, the arterial pressure rises as a result of sympathetic activity. This spontaneous activity is generally referred to the "vasomotor centre," a point in the floor of the fourth ventricle.

It has been described as being rather like the office of the managing director of a commercial enterprise. There is a growing tendency to view this centre as of not much more importance than a telephone exchange through which most of the incoming and outgoing messages pass. There is no doubt, for example, that all strong sensory stimuli

which normally destroy the chemical transmitter ; and in the present instance would cite the fall in the amine oxidase content of vessels after sympathetic denervation. It is important to note, however, that the regain in tone of the ear arteries of the rabbit after sympathetic denervation is not impaired by removing the adrenals or hypophysis (Grant, 1935 ; LeCompte, 1941). If the regain of tone is due to increased responsiveness to a vasoconstrictor substance, the source of this substance is neither the adrenal nor the pituitary. The more

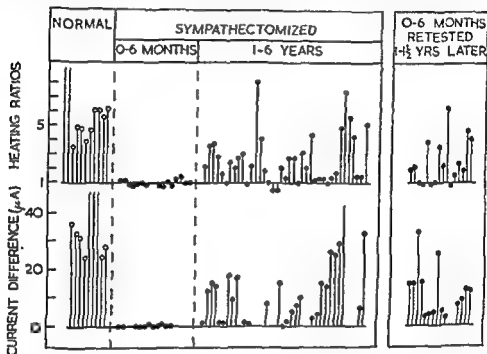


FIG. 4.12. Results of vasomotor and sudomotor tests performed on fifty-six limbs after sympathectomy, arranged from left to right in order of time interval between operation and testing. Vasomotor and sudomotor reflexes were absent in limbs tested six months or less after operation, but returned to normal in limbs tested one to six years after operation. The results with the blood

Hamilton, G. T. C.
G. T. C. (1948b),

Lancet, ii, 770)

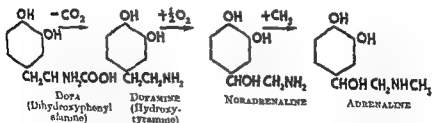
remote effects of sympathectomy are further complicated by regeneration of sympathetic fibres. Fig. 4.12 shows the sizes of the vascular responses to raising body temperature in patients with Raynaud's disease, at various intervals after excision of the inferior cervical and upper dorsal ganglia.

When preganglionic fibres, such as the white rami, alone are sectioned, the ganglion cells and their postganglionic fibres survive. Removal of the ganglia leads to degeneration of the postganglionic fibres. There is some evidence that vessels denervated by ganglionectomy are more sensitive to adrenaline than those denervated by pre-

Stimulation of the preganglionic fibres causes the release of acetylcholine from the ganglia, and there is good evidence that it is this release which excites the ganglion cells and their postganglionic fibres. Excitation of the ganglion cells can be inhibited by nicotine, a device much loved by Langley to map out the distribution of excitatory fibres originating in the several ganglia.¹ It can also be inhibited by the quaternary ammonium compound tetraethyl ammonium chloride (or bromide), and by the penta- and hexamethonium compounds now so much used in the treatment of hypertension (see p. 324). These are known as ganglion blocking compounds, because they block ganglionic transmission from pre- to post-ganglionic fibres.

Adrenaline and Noradrenaline. Postganglionic transmission was for long held to be due to sympathin, which Cannon believed was of two kinds: E, which was mostly excitatory, and I, which was mostly inhibitory. Very strong evidence has now accumulated that postganglionic transmission in the sympathetic system is very largely effected by adrenaline and its close relative noradrenaline, and that of these two noradrenaline is the more important (for review see v. Euler, 1931a). Neither of these corresponds exactly to sympathin E and I. The only other sympathomimetic amine that has been isolated from living tissues of mammalia is hydroxytyramine (dopamine), though other amines can be formed in the gut by decarboxylation.

As to the way in which adrenaline is synthesized:



Hydroxytyramine has been obtained from heart and adrenals and is the chief sympathomimetic amine in urine. Its circulatory action is weak, only $\frac{1}{10}$ to $\frac{1}{100}$ that of L-noradrenaline.

¹ And which prompted the following lunatic which appeared in *Brighter Biochemistry* at Cambridge when I was an undergraduate.

"There was a young man of East Anglia
Whose nerves were a tangle of ganglia;
As —

and many emotions influence sympathetic tone and adrenal activity, and some of these no doubt employ the channels through the vasomotor centre. As we shall see in Chapter 5, the high arterial pressure that results from section of the carotid sinus and depressor nerves is absent in the unanæsthetized animal when it is quiet or asleep. Rather more debatable are the pressor effects of oxygen lack and CO_2 retention, as seen in asphyxia. Although oxygen lack and CO_2 retention quicken the heart and raise arterial pressure by exciting the chemo-receptors of the carotid body, the main effect of these changes in chemical composition is apparently on the central nervous system itself. Over-ventilation leads to a fall of arterial pressure due to diminution in sympathetic tone.

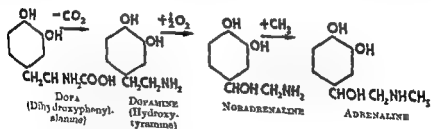
Section of the brain stem at the upper border of the fourth ventricle, above the vasomotor centre, leaves the arterial pressure unaltered. Section below produces a profound fall. Slowly, however, the arterial pressure recovers, though to a lower level, and sympathetic tone is now under the control of spinal "centres." Over-ventilating such a preparation again lowers arterial pressure and this effect can be prevented by the addition of CO_2 to the air used for ventilation (Dale and Evans, 1922). In controlling the activity of the vasomotor centres CO_2 seems much more important than oxygen. That the common factor in this central control of the circulation is the pH in the region of the vasomotor centre is quite unproved.

Chemical Transmission in the Sympathetic-adrenal System

That the autonomic nerves might produce their effects by releasing at their terminations chemical substances with specific affinity for the receptor substances of the motor units activated was first suggested by T. R. Elliott in 1904 when he noted the similarities and the difference between stimulation of the sympathetic nerves and the effects of adrenaline. Proof was first given by Loewi (1921), who showed that when two frogs' hearts were perfused in series with saline, stimulation of the vagus to the first heart would, after a short delay, cause slowing of the second. It soon became apparent that the actions produced by the parasympathetic nerves closely resembled those of acetylcholine, while those produced by sympathetic stimulation closely resembled those of adrenaline, though there were important and undoubted exceptions. That these nerves did undoubtedly liberate these substances, or something very like them was shown by Dale, Cannon and their fellow workers. Since, however, the nerves liberating these substances were not strictly distributed in parasympathetic or sympathetic systems, Dale suggested the use of the terms cholinergic for nerve fibres which release acetylcholine, and adrenergic for fibres which release adrenaline or a close relative.

Stimulation of the preganglionic fibres causes the release of acetylcholine from the ganglia, and there is good evidence that it is this release which excites the ganglion cells and their postganglionic fibres. Excitation of the ganglion cells can be inhibited by nicotine, a device much loved by Langley to map out the distribution of excitatory fibres originating in the several ganglia.¹ It can also be inhibited by the quaternary ammonium compound tetraethyl ammonium chloride (or bromide), and by the penta- and hexamethonium compounds now so much used in the treatment of hypertension (see p. 324). These are known as ganglion blocking compounds, because they block ganglionic transmission from pre- to post-ganglionic fibres.

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Hydroxytyramine has been obtained from heart and adrenals and is the chief sympathomimetic amine in urine. Its circulatory action is weak, only $\frac{1}{10}$ to $\frac{1}{100}$ that of L-noradrenaline.

¹ And which prompted the following limerick which appeared in *Brighter Biochemistry* at Cambridge when I was an undergraduate

"There was a young man of East Anglia
Whose nerves were a tangle of ganglia
As was his - - - - -"

L-Noradrenaline (NOR = "N ohne Radikal," so-called because it differed from adrenaline in the absence of a CH_3 group attached to the nitrogen) seems to be the chief sympathetic transmitter. The sympathetic chain of man contains 2.4 to 3.4 $\mu\text{g.}$ of noradrenaline per gramme and about $\frac{1}{20}$ of this amount of adrenaline. The venous blood leaving the spleen of the cat contains up to 0.5 $\mu\text{g./ml.}$ noradrenaline and up to 0.01 $\mu\text{g./ml.}$ adrenaline after stimulation of the splenic (sympathetic) nerves (Peart, 1949). The effect on most organs of stimulating the sympathetic nerves resembles the action of noradrenaline more closely than that of adrenaline. Von Euler (1951b) found that in 20 adult healthy males the average daily excretion was 29.0 $\mu\text{g.}$ of noradrenaline and 11.5 $\mu\text{g.}$ of adrenaline. Only about 2.4 per cent. of the noradrenaline infused into a vein was recovered in the urine in excess of the normal excretion. These figures should not be accepted as giving more than the vaguest notion about the amounts of those amines liberated at the nerve endings of the normal human subject.

Adrenaline and noradrenaline seem to be fairly stable in blood *in vitro*, but are rapidly removed *in vivo*, chiefly apparently by the action of the kidney. Three possible modes of destruction are known :

(a) Oxidative deamination by amine oxidase (see Blaschko, 1952). Although the extent to which this enzyme is concerned is not known, the idea that it may be the main mechanism of destruction at the sites of action of the amines is supported by the increase in sensitivity conveyed by substances such as ephedrine and tyramine, which may compete selectively for the enzyme, and by the association between the increase in sensitivity to the amines and decrease in oxidase content of organs after sympathetic denervation.

(b) By conjugation and excretion in the urine as ethereal sulphates.

(c) Oxidation to adrenochrome by phenolases.

The relative importance of these three mechanisms is not accurately known ; but it is rather generally believed that the noradrenaline and adrenaline released at the postganglionic endings are destroyed by amine oxidase, in the same way as acetylcholine released at the cholinergic nerve endings is destroyed by cholinesterase. Urine contains the bases in three forms : free, as ethereal sulphates and as glucuronides.

The active substance in the secretions of the adrenal medulla has been traditionally regarded as adrenaline, but it is now known that a varying amount (about 25 per cent.) of the pressor activity is due to noradrenaline (see Table 20 . 4).

Folkow and v. Euler (1954) have shown that hypothalamic stimulation in the cat increases the urinary excretion of adrenaline and noradrenaline according to the location of the stimulus. It is suggested therefore that the adrenaline and noradrenaline secreting cells of the suprarenal medulla are separately innervated.

Comparison of the Actions of adrenaline and L-noradrenaline on the Circulation

The following account is based on infusions of 10 to 40 μ g. per minute into adult human subjects. The subjective sensations are much more unpleasant with adrenaline than with noradrenaline; with the former a curious feeling of expectancy or apprehension is followed by hyperventilation, palpitations and tremor; with similar doses of noradrenaline, these feelings are absent. Adrenaline produces a sustained rise of systolic pressure with unchanged or lowered diastolic pressure, preceded by a transient rise and fall of both values. Noradrenaline produces a rise of both pressures. The heart usually quickens with adrenaline and extrasystoles are not infrequent. With noradrenaline, the heart slows through vagal action, and auriculo-ventricular dissociation may occur (Barcroft and Konzett, 1940; Barnett and others, 1950). Adrenaline greatly increases cardiac output, noradrenaline produces no change (Goldenberg and others, 1948). Adrenaline increases muscle blood flow, the increase being large for a few seconds and later about double. Noradrenaline produces little change, or a rise or a fall. Both substances blanch the skin and greatly decrease skin flow and both decrease renal blood flow, without greatly influencing glomerular filtration rate (Barclay, Cooke and Kenney, 1947; Barnett and others, 1950), but in both skin and kidney, adrenaline is somewhat more active than noradrenaline.

These effects are summarized in the following table, which is illustrative only (Barcroft and Swan, 1953).

TABLE 4.2. *Blood Flow Changes Induced by Infusions of Adrenaline and Noradrenaline.*

	BLOOD FLOW				
	Before	During			
		Adrenaline		Noradrenaline	
		ml/min	% change	ml/min	% change
Liver	1,500	3,000	+ 100	1,500	0
Kidneys	1,500	900	- 40	1,200	- 20
Skeletal muscles	1,000	2,000	+ 100	1,000	0
Braun	750	900	+ 20	675	- 10
Total	4,750	6,800	+ 40	4,375	- 8

It has been shown by Barcroft and his colleagues (see Barcroft and Swan, 1953) that adrenaline and noradrenaline, infused into the brachial artery, both constrict the skin vessels, while adrenaline dilates muscle vessels and noradrenaline constricts them. There are however certain differences between the effects of arterial and venous infusions which may be reflex effects from the baro-receptors stimulated by the rise of arterial pressure induced by the intravenous infusion. De Lary and others (1950) have investigated the circulatory effects of mixtures of the two substances and have found that with equal parts, the adrenaline effect predominates, while the opposing effects balance with mixtures containing three to eight parts of noradrenaline for each part of adrenaline.

To summarize these differences, it may be said that noradrenaline has a fairly generalized constrictor effect on blood vessels (except on the coronaries, which it dilates) and that its pressor effect is wholly due to a rise in peripheral resistance, while adrenaline acts chiefly as a redistributor of blood and as an augmentor of the cardiac output, the rise of systolic pressure being due to this cause and not to a rise in the peripheral resistance. These two different actions may be correlated with the function on the one hand of noradrenaline as the chief chemical transmitter of the sympathetic nervous impulse, and thus largely concerned in the reflex control of the circulation, and on the other of adrenaline as the dominant secretion of the normal adrenal gland, concerned in preparing the body for emergency.

Not all the postganglionic fibres of the sympathetic are adrenergic. The nerves to the sweat glands and the vasodilator fibres to muscle are cholinergic, as may be some of the vasodilator fibres to skin.

2. The Parasympathetic Nerves

The parasympathetic nerves are mainly of local importance, though there is some evidence that they, too, participate in vascular reflexes. The chorda tympani to the salivary glands, the lingual nerve to the tongue and the nervi erigentes are all vasodilator, and cholinergic. The vagus nerves (also cholinergic) are constrictor to the coronary arteries.

3. The Antidromic Nerves

Bayliss (1901) showed that stimulation of the posterior roots produced vasodilatation in the area of skin supplied by these nerves. Lewis and Marvin (1927) showed that this vasodilatation was produced by the liberation of a vasodilator substance at the nerve endings. Lewis (1927) and his colleagues, in their classical experiments on the reaction of the skin to injury, had shown conclusively that one element in the triple response to injury was the flare, an arteriolar vasodilatation

surrounding the point of injury and mediated through a local axon reflex of the nerve fibres of the posterior root system.

So far as is known this axon reflex, possibly excited by the release of histamine from the damaged cells, is the chief or sole function of the so-called antidromic fibres. Lewis and Marvin thought the substance released on antidromic stimulation was histamine or something closely resembling it, since it was relatively stable in the tissues. Dale and Gaddum (1930) provided evidence that antidromic stimulation released acetylcholine. Holton (1953) has recently shown that antidromic vasodilatation is reduced by eserine, and other cholinesterase inhibitors which potentiate that of acetylcholine and do not affect that of histamine. It now seems possible that this chemical transmitter may be adenosine triphosphate (ATP) which Holton and Holton (1952, 1953) have found to be present in extracts of dried spinal roots, in quantities sufficient to account for their vasodilator action. ATP injected intra-arterially into the rabbit's ear also produces a vasodilatation closely resembling that of stimulating the great auricular nerve.

Brown and Maycock (1940) were unable to find any evidence for the participation of antidromic fibres in vascular reflexes in the sympathectomized cat.

4. The Renin-hypertensin System

Renin was discovered in 1898 by Tigerstedt and Bergman, who obtained prolonged rises in arterial pressure in the anaesthetized rabbit by injecting saline extracts of fresh rabbits' kidneys or of the residue left by extracting kidneys with alcohol. Tigerstedt and Bergman correctly described the properties of renin, its distribution in the kidney, the potentiation of its effect by nephrectomy, and its action on the pithed animal. Yet for the next forty years only Bingel and his colleagues (Bingel and Strauss, 1909, Bingel and Claus, 1910) confirmed these findings. Many others, such as Shaw (1906) and Pearce (1909), failed. Hartwich and Hessel (1932) claimed to have obtained renin, but the properties of their product, extracted from autolysed kidneys, were those of the putrefactive amines. In 1936, when Prinzmetal and I first obtained pressor responses with renal extracts, renin was not known.

book of physiology. It

been adequately explain

in the relationship between disease of the kidney and hypertension.

for this

from the use of anaesthetized animals for testing extracts and provided evidence that anaesthetics may interfere with renin's

action. This effect, noted in the rabbit for urethane by Bingel and Claus (1910), was confirmed for ether by Scarff and Martin (1941). Goldblatt, Lamfrom and Haas (1953) have shown that in the dog the responses to both renin and hypertensin are reduced by ether, nembutal, chloralose and morphine. However this may be, 1938 saw the beginning of new interest in renin with publications from Landis, Montgomery and Sparkman; Hessel; and Pickering and Prinzmetal.

A very full account of renin will be found in the book by Braun-Menendez and others (1946). Renin has only been obtained from the cortex of the kidney. It is absent from the medulla and all other tissues investigated. In the cortex it is present in the superficial layers from which glomeruli are absent (Taquini and others 1950). Its source is therefore thought to be the tubules. It has been found in most mammals, birds, amphibia and fishes examined, including the aglomerular fish.

Renin has not been obtained pure. The purest preparation (Haas and others, 1953) contains 780 Goldblatt units of renin per mg. dry substance. It has the properties of a protein, separating with the globulin fraction. It is non-dialysable, destroyed by boiling, by heating to 58° C. for twenty minutes, and by alcohol and acetone at room temperature, though not in the cold. Thanks to the work of Page, Braun-Menendez and their colleagues, it is now known that renin does not itself cause vasoconstriction. It acts as an enzyme, splitting off from hypertensinogen one of the α_2 globulins of the plasma, a much smaller molecule, hypertensin, or angiotonin, which is the pressor substance. This reaction between renin and hypertensinogen follows the ordinary laws of enzyme action, the velocity of the reaction depending on the concentration of the enzyme (renin), the amount of the product (hypertensin) formed in infinite time on the amount of the substrate (hypertensinogen). Ordinarily this relationship is upset by the presence of another enzyme, hypertensinase, which destroys hypertensin.

Hypertensinogen is an α_2 globulin. Its concentration in plasma remains fairly constant under normal conditions, but is reduced by the injection of renin, or by falls of arterial pressure which stimulate the secretion of renin by the kidneys. Tachyphylaxis, the reduction and final extinction of the response to rapidly repeated injections of renin, may be due to exhaustion of hypertensinogen but may occur without any fall in plasma hypertensinogen (Goldblatt and others, 1953). Hypertensinogen is formed by the liver, for when the plasma content has been reduced by renin, it regenerates in normal time if all the viscera except the liver are removed, but not at all if the liver is excluded (Braun-Menendez and others, 1946).

Hypertensin has not yet been obtained pure. It is a smaller

molecule than either of its forerunners, since it dialyses freely through cellophane. This implies that its molecular weight is probably less than about 10,000. Studies on its rate of diffusion have suggested a molecular weight of 1,000 or less (Edman and others, 1942). In crude solution it is stable to boiling at neutral or acid pH, but is more rapidly destroyed at alkaline pH. At 20° C. it is stable for at least three hours from pH 1 to 12. Purification leads to increased lability, though the reasons for loss of activity have not been established in each case. In an electrical field, it has been shown to behave as a "zwitterion", moving to the cathode at acid pH and to the anode at alkaline pH. The iso-electric range is 7.0 to 8.5, as determined by paper electrophoresis (Peart, unpublished); previously it had been reported as 6.8 (Edman and others, 1942). The main controversy has been whether hypertensin is or is not a peptide. Clark (1951) has claimed to have obtained highly active fractions on chromatography which did not give a colour with ninhydrin and which did not produce amino acids on hydrolysis. The quantities of hypertensin involved were not stated and as the preparation might still have had little hypertensin present this evidence is inconclusive. The evidence in favour of a peptide structure is more convincing though still indirect. Its precursors are two proteins, it behaves as a zwitterion in an electrical field, and its activity is destroyed by trypsin and chymotrypsin. Many peptides do not give a colour with ninhydrin (Bricas and Fromageot, 1953), so that on balance it is still most likely that hypertensin will prove to be a peptide. Bumpus and Page (1954) claim to have isolated such a peptide and have reported on its amino-acid constitution. Peptides associated with pressor activity having a different amino acid composition have been obtained by Skeggs, Marsh, Kahn and Shumway (1954) and Peart (unpublished). The number of amino acid residues in the peptide varies from eighteen in the case of Bumpus and Page to nine in the product isolated by Skeggs and others.

Hypertensinase is the enzyme destroying hypertensin. It is probably a protein and is precipitated with ammonium sulphate between 0.3 and 0.6 saturation. It is inactivated in a few minutes at pH 7 by heating to 60° C., or in twenty minutes at 25° C. at pH 3.6 to 3.9. Very small amounts are present in plasma, large amounts in cells, particularly those of intestinal mucosa, kidney and red cells. As a consequence, most crude preparations of renin contain it, as does most serum obtained from the slaughterhouse, because of hæmolysis. Its effects on the renin-hypertensin reaction can be avoided by previous acidification, or by conducting the reaction at 0° C., when hypertensinase is nearly inactive (Bean, 1944; Sapirstein, Reed and Southard, 1944).

Action of Renin and Hypertensin. If renin is injected intravenously in doses which produce rises of pressure of about 40 mm. Hg, the rise of pressure does not begin for about thirty seconds, reaches a peak in two minutes and lasts upwards of thirty minutes. Hypertensin produces a quick response, beginning in about fifteen seconds and maximal at twenty to forty seconds, and over in three or four minutes. The differences in time relations can be attributed to the persistence of renin in the blood stream and to the time taken for its reaction with hypertensinogen. The fate of the renin itself is not known. It is fairly stable in blood *in vitro* and very little is excreted in the urine (Houssay, Braun-Menendez and Dexter, 1942; Pickering, Prinzmetal and Kelsall, 1942). *In vivo* its rate of disappearance from blood is reduced by removal of the kidneys, by removal of the liver, and very much more conspicuously by uræmia, which gradually supervenes after bilateral nephrectomy (Braun-Menendez and others, 1946). In animals with and without anaesthesia, frequently repeated injections of renin produce diminution and finally extinction of the pressor response (tachyphylaxis), due partly, as has been noted, to consumption of hypertensinogen. In the unanaesthetized rabbit and dog, if sufficient time is given for the arterial pressure to return to normal, fairly constant responses are obtained (Pickering and Prinzmetal, 1938a; Goldblatt and others, 1953).

Renin has been obtained from the kidneys of all mammals examined and from those of birds, but the results from fish are contradictory. There is some species specificity. Thus man is refractory to renin from species other than primates, human hypertensinogen in fact reacts only with primate renin. On the other hand, renin from man and other primates acts on the hypertensinogen of other mammals. Birds appear to have a renin which acts only on the hypertensinogen of birds (Braun-Menendez and others, 1946).

The pressor effect of renin, mediated through hypertensin, is due to vasoconstriction, for as Tigerstedt and Bergman (1898) noted first for renin, and as has been confirmed, there is no action on the heart. In man, a single injection of impure hypertensin produces a rise of systolic and diastolic pressures, a slowing of the heart, a fall in cardiac output, an increase in heart size, a rise in venous pressure, a fall in vital capacity, and a small fall in skin temperature and forearm blood flow. Continuous infusions produce similar but less striking changes (Bradley and Parker, 1941; Wilkins and Duncan, 1941). Corcoran, Kohlstaedt and Page (1941) found that hypertensin in doses sufficient to raise the arterial pressure by about 40 mm. Hg reduces the effective renal blood flow by about 50 per cent., but lowers the glomerular filtration rate to a much less extent, changes attributed to efferent glomerular arteriolar constriction.

The effects of these substances in the experimental animal are in the main similar to those in man. In the rabbit their action is completely unlike that of adrenaline, noradrenaline and pituitrin in that they produce no paling of the ears, except in very large doses, and no change in skin temperature. The capillaries and arteriovenous anastomoses of the rabbit's ear seem largely unaffected and the main effect is on the arterioles, as can be established by inspection and measurement (unpublished observations). Since the pressor effect persists after pithing, the action of these substances is on the peripheral vessels themselves, though the nature of the receptor substance has not been investigated.

Renin and hypertensin have peculiar and striking effects on renal function. In the unanæsthetized rabbit they produce a diminution followed by an enormous rise in the output of urine, which after renin may rise from 1 or 2 ml to 50 ml in half an hour. The urine during the diuresis is peculiar in that its chloride and sodium concentrations approximate to, and tend slightly to exceed, those of plasma. The preliminary antidiuretic effect may be due to renal vasoconstriction, since glomerular filtration rate is apparently reduced during this phase. The later diuretic effect is associated with a normal glomerular filtration rate and with a reduced renal blood flow and raised filtration fraction, to be interpreted as due to efferent glomerular arteriolar constriction. Nevertheless, the diuretic effect seems not to be due to these changes, since it often outlasts them. It would seem to be due to a specific effect on the distal tubule inhibiting the differential reabsorption of water, sodium and chloride (Pickering and Prinzmetal, 1940; Brandt and Gruhn, 1948; Hughes-Jones and others, 1949). Similar effects have been observed in the rat (Sellers and others, 1952).

That renin induces proteinuria was also noted by Pickering and Prinzmetal and confirmed by Addis and others (1949). The protein, which appears to be plasma protein (Sellers and others, 1952), seems to gain access to the urine largely through *increases* in glomerular *permeability*, prevented by

nephrectomy, *and* Houssay (1898) found. This effect develops gradually over the course of at least two days. Houssay and Dexter (1942) attributed this effect to a combination of increase in vascular reactivity, increased hypertensinogen, and to a longer persistence of renin in the blood. The slow disappearance of renin in the nephrectomized animal seems to be due to a tissue change associated with uræmia. As we shall see in the chapter on experimental hypertension (Chapter 5), this effect is of considerable importance and has not been sufficiently elucidated.

In that same chapter the assay of renin, the effects of prolonged infusion and its relation to hypertension will be discussed.

Renin probably exists in the kidney in a combined form. Pickering and Prinzmetal (1938a) showed that, as it exists in the kidney, it resists the action of alcohol and Williams, Grollman and Harrison (1941) have found that by freezing and rapid drying of kidney they obtained preparations which did not become reactive until some minutes after contact with water.

Hamilton and Collins (1942) showed that in the dog, lowering the arterial pressure by hæmorrhage, or histamine, liberated into the blood a pressor substance from the kidney, and provided evidence that this was renin, since such animals became refractory to injected renin. They also showed that a given hæmorrhage produced a bigger fall of arterial pressure when the renal pedicle was tied. Huidobro and Braun-Menendez (1942) demonstrated that bleeding or intestinal manipulation increased the renin content of the arterial blood, even after denervation of the kidney; KCN and breathing 8 per cent. oxygen did not do so unless they lowered arterial pressure. That renin is released from the kidney by occluding or greatly narrowing the renal artery will be shown in Chapter 5. Thus there is no doubt that the renin-hypertensin system is concerned in the regulation of arterial pressure. Whether the stimulus to the release of renin is fall of intravascular pressure, fall of blood flow, or fall of pulse pressure, or indeed some other effect, is uncertain.

Function. The renin-hypertensin system would thus seem to be comparable with the carotid sinus and depressor reflexes as a homeostatic mechanism for the regulation of arterial pressure (Pickering, 1943). In this instance the regulation would seem to be primarily in the interests of glomerular vascular pressure on which the secretion of urine ultimately depends. While the needs of the heart and brain are immediate, for a very short fall of arterial pressure produces loss of consciousness, and therefore demand a rapidly acting reflex mechanism, those of the kidney are adequately met by a slower mechanism. The renin mechanism would seem admirably designed for this purpose. For the substance actually released into the renal circulation is not active and hypertensin is produced only slowly in the general circulation. The renal vessels thus receive no more of the active agent than they would of one whose ultimate origin was from another tissue.

5. Pitressin

The secretions of the posterior lobe of the pituitary comprise two substances at least, pitressin with an action on the circulation, smooth muscle generally and the excretion of water, and pitocin acting on the pregnant uterus. These have recently been isolated as peptides and

their amino-acid structure demonstrated by Du Vigneaud and others (1953). Since Oliver and Schafer (1895) demonstrated that extracts of the posterior lobe of the pituitary raised the arterial pressure of the anesthetized animal, it has been customary to think of the posterior pituitary secretion as an important circulatory hormone. This is probably a false view and there is little doubt that its chief function is that of regulating the renal excretion of water, its secretion being regulated by the osmoreceptors demonstrated by the beautiful experiments of Verney (1946). In the experimental animal pitressin in large doses raises the arterial pressure by constricting arterioles and capillaries, the cardiac output often being reduced and the coronary arteries constricted to an extent which, it is thought, may weaken the force of the heart beat. A second injection often causes a fall of arterial pressure that is said to be of cardiac origin. In man its most conspicuous effect is to blanch the skin by constricting the minute vessels. Doses producing such an effect may have no significant action on the arterial blood pressure, though they do conspicuously reduce the volume of urine (Sacks, 1924, Theobald, 1934).

Krogh's hypothesis that pitressin might regulate capillary tone may apply to amphibia, but not to man (Lewis, 1927). Pitressin is apparently released in the fainting attack and may in part account for the conspicuous pallor that accompanies it (see Chapter 3).

6. The Hormones of the Adrenal Cortex

One of the classical signs of Addison's disease is low blood pressure. The administration of adequate doses of sodium may raise the pressure, but this is more easily and surely accomplished by adequate doses of Desoxycorticosterone or the naturally occurring steroids of the adrenal cortex, overdosage with these substances will produce hypertension and oedema. Adrenalectomized animals are extremely sensitive to intravenous injection of histamine and anaphylactic shock. These and other phenomena suggest that the steroids of the adrenal gland exert an important effect on the circulation. Now part of it is

...has been put forward by ... and his colleagues. They found that the muscular weakness of adrenalectomized dogs could not be demonstrated in the excised and artificially stimulated diaphragm. They therefore thought that the weakness might have a circulatory cause and found in the adrenalectomized dog that the contractibility of exhausted muscles could be restored by raising the arterial pressure by 60 to 80 mm. Hg by injection of noradrenaline, the contractibility being maintained until the

pressure fell. They showed that the blood pressure response to an intravenous injection of noradrenaline was decreased in the adrenalectomized dog, in which also continuous infusions of noradrenaline failed to produce sustained hypertension, the arterial pressure falling to shock levels. A single injection of adrenal cortical extract but not of desoxycorticosterone would potentiate the response to noradrenaline in adrenalectomized animals but not in normal controls (Ramey, Goldstein and Levine, 1951). Fritz and Levine (1951) found that the vessels of the meso-appendix of the adrenalectomized rat became refractory to the repeated application of noradrenaline while those of the normal rat did not and that the responsiveness was restored by 11-oxysteroids injected intramuscularly, or applied locally in much smaller doses. They conclude that C_{11} -oxysteroids are necessary for the blood vessels to respond optimally to sympathin E. They consider that the normal circulatory adjustments to such changes as muscular activity and anoxia involve vasoconstriction in inactive areas that is mediated through the sympathetic nerves. In the adrenalectomized animal the vessels become refractory to the continued action of the sympathetic transmitter, noradrenaline, and thus the non-active areas, instead of having vasoconstriction, have vasodilatation and the circulation fails.

7. Other Vasoconstrictor Substances

Collip's Substance. In 1928 Collip reported the presence of a pressor substance in extracts of all tissues examined. The extracts were made with boiling water and, after concentration *in vacuo*, were extracted with acetone. Intravenous injection of amounts corresponding to considerable weights of tissue produced a rise of blood pressure lasting about ten minutes. The effect is antagonized by cocaine and reversed by ergotoxin. What part, if any, this substance plays in the body is unknown.

Serotonin, 5-hydroxytryptamine. It has been known for many years that vaso-active substances appear in blood when it clots. Freund (1920) distinguished two: "Frühgift", vasodilator, appearing early and stated by Zipf (1932) to be adenylic acid, and "Spätgift," a vasoconstrictor appearing later. The vasoconstrictor was subsequently isolated by Page, Rapport (1949) and co-workers, recognized as 5-hydroxytryptamine combined with creatinine and sulphate, and identified with the synthetic product of these components (for full review with literature, see Page, 1954). This proved identical with the enteramine of Erspamer and Asero (1932) obtained from argentophile cells of the gut in mammals, the posterior salivary glands of the octopus and elsewhere. Injected intravenously into dogs anesthetized with pentobarbital, serotonin usually produces a fall of pressure with brady-

cardia, succeeded by a sustained rise and finally a prolonged fall, but the effect is dependent on the anaesthetic used. Even under deep anaesthesia, one of the most pronounced effects of serotonin is to cause evacuation of the bowels, increased peristaltic sounds and increased tone of the bladder wall. It has a powerful constrictor action on isolated arterial rings. In man intravenous injection produces a transient fall of pressure followed by a rise or fall, transient hyperpnoea, and numerous subjective sensations including a desire to empty bladder and bowels. Serotonin may be concerned in the local vascular spasm associated with injury, thrombosis and embolism. Erspamer believes it is concerned with gastro-intestinal activity.

Long-acting Renal Substance Shipley, Helmer, and Kohlstaedt (1947) have obtained in 2-day nephrectomized cats very prolonged pressor responses from the plasma of cats, in which the arterial pressure had been low for a long time due to infection, poisoning, or hæmorrhage. The substance appears to be of renal origin, for it is not obtained from the plasma of nephrectomized animals similarly treated. Helmer and Shipley (1947) have shown that the substance is more slowly destroyed by the nephrectomized animal than is renin.

8. Vasodilator Substances

While the vasoconstrictor substances seem in general designed to affect the organism as a whole after their release into the general circulation, the vasodilator substances appear to be chiefly concerned in local circulatory regulation by dilating the vessels at, or near, their site of release. An interesting review of these substances was given by Dale (1933).

Acetylcholine Acetylcholine injected intravenously produces a

dilator fibres in the sympathetic ganglia, of the vaso-
some sympathetic re-
transmitter in the i-
glands. Its extremely rapid destruction by the cholinesterase present both at the nerve endings and in the blood suggests that it has no other than a strictly local function.

Histamine. Histamine has been extracted from most tissues; much is present in skin and lung, little in muscle. It is present in blood chiefly in white corpuscles. In the organs and in the blood it probably exists in molecular combination as an inactive substance. In human urine it is chiefly excreted as acetyl-histamine. Adam, 1950.
mine is rele-

that the local vascular response—the triple response—is due to this release. Feldberg and Paton (1951) have confirmed this by direct estimations on the blood leaving perfused skin. Histamine is also released from the cells in local and general antibody—antigen responses underlying the immediate type of allergy and anaphylaxis. It has been suggested that it is the local vasodilator concerned in reactive hyperæmia and in exercise, but the evidence is inconclusive and the latter is rendered unlikely by the small quantity of histamine in muscle.

Adenylic Acid Compounds. The conversion of adenosine triphosphate to adenosine diphosphate and *vice versa* is one of the main sources of the transfers of energy required in the enzymic catalysis of cellular metabolisms. Adenosine, and adenylic acid injected intravenously produce a fall of blood pressure, arteriolar dilatation and heart block, and after intraperitoneal injection a leucocytosis (Bennet and Drury, 1931). The amounts required are large, 0.6 mg. to give a fall of 20 mm. Hg in the cat, and 50 mg. to double the white cells in the rabbit. Adenylic acid compounds may well prove the vasodilator substances in exercise, but there is no proof (see also p. 69).

Kallikrein is the name given by Frey and Kraut (1926) to a protein-like substance obtained from normal urine and first described by Abelous and Bardier (1909) as urohypertensin. It is precipitated by half-saturated ammonium sulphate, is non-dialysable and destroyed by boiling. It is rapidly inactivated by blood, a process which is said to be due to the formation of an inactive compound which can release kallikrein when the reaction is acid. It has been thought to be manufactured in the pancreas, since pancreatectomy reduces the urinary excretion—but insulin apparently restores it. Kallikrein produces a fall of arterial pressure on intravenous injection, due to arterial dilatation since the heart's action is augmented. Whether kallikrein is of purely local, or of general, importance is still unknown.

Substance P of von Euler and Gaddum (1931) is another complex substance of high molecular weight, having vasodilator properties. It is present chiefly in brain, stomach and intestine, hardly at all in muscle, spleen, lung, liver, kidney or pancreas. Its function is unknown.

Hydrogen Ion Concentration and CO₂. The acids formed during metabolism have long been known to be vasodilator, and were at one time thought of as the chief dilator products of cellular activity. Probably their role is a modest one. Fleisch and Sibul (1933) found that addition of CO₂ to blood to the extent of raising acidity by 0.05 pH unit doubled the blood flow. Lactic acid was dilator in the perfused hind limb of the cat entirely by its effect on pH. Gollwitzer-Meier (1950) has shown that the pH changes of blood leaving muscle during and after contraction are complicated and not proportional to blood flow.

THE REGULATION OF BLOOD FLOW TO THE INDIVIDUAL TISSUES

Having considered the regulation of the circulation in general, and the individual mechanisms known to regulate the peripheral vessels, we may now consider the regulation of the circulation to the individual organs. This is an important aspect of our subject because, as we have seen, it is in the tissues themselves that the function of the circulation is accomplished, and this is true whatever the height of the arterial blood pressure.

The Brain

The cerebral arteries are amongst the feeblest in the body, having poorly developed muscular coats. They contract very feebly to stimulation of the cervical sympathetic nerves and to adrenaline (Fig 4.9); adrenaline applied locally constricts the pial arteries, but injected intravenously dilates them, because the feeble contraction is overcome by the rise of arterial pressure. In normal man, anaesthetization of both stellate ganglia, with consequent interruption of most or all of the sympathetic impulses to the cerebral vessels, produces no increase in the blood flow (Harmel and others, 1949). Roy and Sherrington (1890) showed that cerebral blood flow is intimately dependent on the general arterial pressure, and is further regulated by vaso-active substances produced locally. Which vasodilator substances are particularly involved is not known. The cerebral vessels participate only slightly in the vascular adjustments initiated by the carotid sinus mechanism, which may be regarded therefore as a device to safeguard cerebral blood flow (Heymans and others, 1933).

The Heart

In the isolated denervated heart lung preparation Starling (1912) showed the very close relationship between arterial pressure and coronary flow. Thus in a dog's heart expelling 1,400 ml. per minute at a

coronary pressure of 60 mm.

mm. Hg

Lowering the oxygen tension of the blood increases coronary flow, as does stimulation of the sympathetic accelerator nerves or the intravenous injection of adrenaline. Stimulation of the vagus constricts the coronary arteries. Increased cardiac work in the isolated denervated organ is associated with increased flow, presumably due to dilator action of substances released during cardiac contraction. It is not known whether these substances are the same as those released during contraction of voluntary muscle.

The Kidney

Glomerular filtration is intimately dependent upon the pressure in, and blood flow through, the capillaries of the glomerular tuft; tubular

excretion and reabsorption are much affected by blood flow through the tubules. Glomerular filtration rate and renal blood flow tend to remain remarkably constant in the resting normal subject, and are relatively little affected by spinal anaesthesia (Smith and others, 1939). The sympathetic thus seems to have very little tonic activity. However, Smith (1939) has shown that the renal vessels do participate in the postural reflexes; renal blood flow and glomerular filtration rate fall to the same degree when the normal subject changes from the supine to the upright posture. After hæmorrhage, renal blood flow may fall very considerably before arterial pressure has fallen, and in the later stages when arterial pressure is low, the fall in renal blood flow may be so pronounced that the kidney is damaged, its function only slowly returning to normal (Van Slyke, 1953).

Gut and Liver

Stimulation of the splanchnic nerves in the experimental animal produces a very large rise of arterial pressure, which is partly but not entirely due to the release of adrenaline. Section of the splanchnic nerves may produce a substantial fall of arterial pressure. These classical experiments were the origin of the idea, held by past generations of physiologists, that the splanchnic circulation was by far the most important element in the regulation of arterial pressure and therefore that overaction of the splanchnic nerves was the cause of hypertension in man, which should therefore be cured by their removal. The idea that human hypertension is due to splanchnic vasoconstriction has now been abandoned by most people (see Chapter 7).

Gut blood flow has not yet been measured in the intact animal, but liver blood flow can be measured by the bromsulphalein clearance method of Bradley and others (1945). Liver blood flow, of course, includes blood arriving via the hepatic artery as well as that by the portal vein. Following splanchnic section liver blood flow increases (Wilkins and others, 1947). The liver blood flow is reduced by change from the horizontal to the erect posture in the normal subject after splanchnic section (Wilkins and others, 1951). In the experimental animal the gut vessels react vigorously in the reflexes regulating arterial pressure (Heymans and others, 1933). In man adrenaline seems to increase liver blood flow; though in the anaesthetized cat and dog it constricts gut vessels and in the dog causes the sphincters on the caval end on the hepatic vein to constrict (Bauer and others, 1932).

The Skin

Stimulation of the sympathetic nerves produces vasoconstriction of arteries, arterioles, capillaries, venules and veins, and arteriovenous anastomoses. These effects are most easily demonstrated in the ear

of the rabbit by stimulating the cervical sympathetic. The vasoconstriction resulting from sympathetic stimulation is probably as great in the skin as in any organ of the body. There is now no doubt that the sympathetic also conveys vasodilator fibres to the skin. Warming the body produces flushing and rise of skin temperature of the human forearm, which is prevented either by sympathectomy or, in the affected territory, by local anaesthetization of the cutaneous mixed nerve as it pierces the fascia (Grant and Holling, 1938).

The skin vessels are chiefly concerned in the vascular reflexes controlling temperature, loss of heat by radiation and conduction, accounting for about 70 per cent. of the heat loss of a normal subject at rest in temperate climates. The arteriovenous anastomoses occurring in large numbers in the nail beds, on the palmar and plantar surfaces of the fingers, toes, hand and foot, and capable of varying quickly their blood flow from very low to very high rates, are particularly important here (Grant and Bland, 1932). Two sets of receptors, one in the skin and one centrally, are concerned in this cutaneous vasomotor control (Pickering, 1932). The skin vessels are probably concerned, like other vessels, in the general reflexes maintaining arterial pressure and arising in the main from baro-receptors in the carotid sinus and aortic arch. Sympathetic tone in the skin at any point of time may be regarded as the sum of these various reflex effects.

The relative effects of heating the body and of suppressing sympathetic impulses differ in the different parts of the paretics. In the hand there is very little difference. In relieving the vasoconstriction of Raynaud's disease, Lewis and Pickering (1931) found warming the body more potent than anaesthetizing the nerves to the hand, but on blood flow Pickering (1938b) and Arnott and Macfie (1948) found no difference between nerve anaesthetization and raising body temperature. In the forearm, warming the body is more potent than nerve anaesthetization, but in the feet of the supine subject suppressing nerve impulses by nerve anaesthetization seems to be more potent than warming the body (Pickering and Hess, 1933). It would thus seem that warming the body causes stimulation of —

sympathetic vasoconstrictor tone. Severing the sympathetic nerves produces full vasodilatation in the skin for one or two days only. Subsequently, skin flow declines, until after ten to fourteen days it is little larger than before operation (Fig. 4.10) (Duff, 1951). This decline in blood flow parallels increase in sensitivity to adrenaline and other agents. In the rabbit's ear this regain of tone happens just the same after adrenalectomy and hypophysectomy (Grant, 1935; LeCompte, 1941). This increase in tone

and increase in sensitivity following denervation is common to most tissues (Cannon and Rosenblueth, 1949).

Owing to their accessibility the reactions of skin vessels are better known than those of most tissues. Adrenaline and noradrenaline constrict arteries, arterioles, capillaries and veins; pitressin produces intense constriction of minute vessels. Acetylcholine, histamine and nicotinic acid are dilator. Lewis (1927) showed that the response to skin injury consists of three parts: a local red reaction, a local increase in permeability and, surrounding arteriolar dilatation, the flare, produced by an axon reflex, and he showed that these three responses are also produced by histamine. Histamine is almost certainly a major agent in the response to injury, but not the only one, as it does not account for the cellular response.

When the circulation to a limb is arrested and subsequently released, the skin flushes brightly and becomes hot, so-called reactive hyperæmia. Lewis and Grant (1925) showed that this vasodilator response of arterioles and minute vessels is independent of the central nervous system, and ascribed it to the dilator action of substances produced locally in the ordinary metabolic activity of the cells. Freeman (1935) has shown that in the hand the reactive hyperæmia following short periods of circulatory arrest discharges the blood flow debt accumulated during the arrest in both normal and sympathectomized hands, but that after periods of arrest longer than twelve minutes, the increase in blood flow exceeds the debt, perhaps because of a new factor, tissue injury. Reactive hyperæmia is an extremely important phenomenon, because it is an expression of the local chemical regulation of the circulation. Some of these vasodilator substances have been discussed (p. 77). Which of them is concerned in reactive hyperæmia in the skin is not accurately known.

Muscle

Stimulation of the sympathetic nerves causes vasoconstriction or weak vasodilatation in the voluntary muscles of animals. Section of the sympathetic nerves about doubles muscle blood flow, the subsequent recovery of tone being very similar to that in the skin (Fig. 4.10). Heating the body also about doubles blood flow in forearm muscle, but has no effect in the sympathectomized limb (Barcroft and others, 1943).

voluntary muscle rises enormously and this increase in flow is not seen in the sympathectomized forearm, or forearm the nerves to which have been blocked with novocaine. In a given subject at the height of the fainting reaction, the blood flow through the normal limb is greater than through that with nerves blocked, suggesting that vasodilator

others (1952) have shown that when muscle blood flow is raised in the resting subject by heating the body or by adrenaline, the increase in blood flow during and after exercise is quite unaltered. This suggests the presence of two distinct and independent circulations through muscle, the one under sympathetic control, the other being more or less exclusively affected by the vaso-active substances liberated during exercise. The muscle vessels probably participate in all vascular reflexes, particularly those of the baro-receptors. As has been seen, the muscle vessels constrict through sympathetic action in the change from horizontal to the upright posture (Fig. 3.2).

This reflex response, mediated through the sympathetic, is small as compared with the effects of reactive hyperæmia and exercise. Most of the capillaries are shut in resting voluntary muscle; in exercise they open (Fig. 4.2). Grant (1938) found in a normal human forearm that the resting flow of 1 ml. per 100 ml. per minute increased to 24 ml. after four minutes' exercise, the normal level being regained in about fifteen minutes. A similar response occurred in the sympathectomized arm. After five minutes' ischaemia, the blood flows were respectively 37 and 41 ml. per 100 ml. per minute on the normal and sympathectomized sides. The actual substances concerned in the response to exercise are unknown. Many of the intermediate metabolites are dilator, but do not reach high enough concentration in the venous blood (Fleisch and Sibul, 1933) to be demonstrated by the methods hitherto used.

SUMMARY

It is clear from this account that the devices regulating arterial pressure and the blood flow to the organs of the body are many and complex and that we are far from understanding them completely. The several mechanisms are almost certainly closely co-ordinated. The behaviour of the sympathectomized dog (p. 63) suggests that there is more than one device to achieve a particular purpose; when the chief device breaks down, the secondary devices may be able to act as substitutes.

Any attempt to summarize this chapter is bound to be

(b) the renin-angiotensin system and the sympathetic-adrenal system

pressure. Little is known of the

mechanism that releases renin ; but its effect is prolonged, and it would seem that the renin-hypertensin system provides a coarser and more slowly acting control of arterial pressure. Of the other vaso-active nerves and substances, it would seem that most are concerned with the local regulation of blood flow, though the adrenal steroids must have a more general function.

The vessels supplying the several organs of the body behave differently to the individual vaso-active agents. These differences of vascular behaviour are interesting from the physiological point of view because they can be correlated with differences in the functions of the individual organs. So far as the theme of this book is concerned, these differences of vascular behaviour are of particular interest because they may provide information as to the nature of the agent by which arterial pressure becomes raised.

CHAPTER 5

EXPERIMENTAL HYPERTENSION

A TIME-HONOURED method of investigating disease is to try and reproduce it in animals. This method has proved of the utmost value, and without it the advances that have taken place all over the front of medicine would not have occurred. Nevertheless, it has the defect of leaving the proof still to be obtained in man. This defect is well illustrated by the present chapter, for whereas the experimental production of hypertension in animals has yielded results of the greatest interest, its relevance to human disease is, in many instances, still not established.

Early attempts to produce hypertension experimentally were hampered by the absence of a method of repeatedly and accurately estimating arterial pressure. Bradford in 1892 studied the effects of excising most of the renal substance in dogs and noted cardiac hypertrophy. Pässler and Heineke (1905), Wood and Ethridge (1933), Cash (1924) and Chanutin and Ferris (1932) made similar observations in dogs and rats. Hering's pupils, Koch and Mies (1920), produced hypertension by cutting the carotid sinus and depressor nerves in the rabbit. These, and several other contributions to be mentioned later, preceded the work of Goldblatt and his colleagues (1934). Nevertheless, it was Goldblatt's work which gave the major impetus to the study of experimental hypertension, partly by introducing an entirely new and challenging method of producing hypertension which seemed at once relevant to the problem in man, partly by the immense trouble taken to establish the facts beyond reasonable doubt.

METHODS OF REPEATEDLY ESTIMATING ARTERIAL PRESSURE IN EXPERIMENTAL ANIMALS

Some of the discrepancy which exists between the reported results of different authors studying the same problem is almost certainly to be attributed to the use of different methods.

Much more satisfactory is the carotid loop of Van Tassell. It is a method of repeatedly estimating arterial pressure in experimental animals.

Goldblatt in his early experiments. Verney and Vogt (1938) denervated the carotid sinus to ensure that compression of the artery should not elicit the reflex.

Probably the most satisfactory method is the direct measurement by femoral artery puncture in trained dogs, as used by Goldblatt in his later work. The dog lies on its back on a special support with the hind limb, that is to be used, tied down. The observer feels the femoral artery and plunges into it a short-bevel No. 20 gauge needle attached to pressure tubing containing sterile isotonic sodium citrate (4 per cent.) leading to a mercury manometer. The needle and adjacent part of the apparatus is sterile. A skilful observer and a submissive dog enables these measurements to be repeated over months and years. The pressures obtained are, of course, mean femoral arterial pressures, since the manometer is heavily damped. Systolic and diastolic readings can be obtained using a high-frequency membrane or capacitance manometer (see Chapter 2).

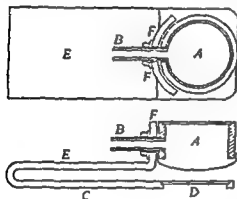


FIG. 5.1. The capsule for estimating arterial pressure in the central artery of the rabbit's ear. *A* is the pressure chamber closed on the top side by a watch glass and on the lower by a loose membrane of thin rubber or "Cargile." *D* is another glass plate. The ear is slipped between the two plates. *C* and *E* are the central artery.

values which should not differ by more than 6 mm. Hg is taken as the reading (Grant and Rothschild, (1934), *J. Physiol.* 81, 265).

The Rabbit. The only known method of repeatedly recording arterial pressures in the rabbit without gross disturbance is that introduced by Von Recklinghausen and perfected by Grant and Rothschild (1934); it uses the central artery of the depilated flushed ear. A rabbit will sit quietly if it is placed on a cloth which is pulled over the body and made firm with a sandbag. The room must be warm (26° C.) so that the ears are flushed. The capsule (Fig. 5.1) is slipped on to the ear so that the central artery lies between the membrane of the capsule and the window in the base plate of the capsule. The pressure is then raised till the pulse fails to reach the top of the artery and then lowered till it first returns; the mean of these two values, which should

noradrenaline (Brackett, Dickerson and Wilson, 1950). In earlier readings on different rabbits the correlation coefficient between pressures estimated by the central artery of the ear and by mercury manometer in the

such a method seems to be personally do not like to accept results obtained with this method confirmed by a better.

measured on the tail and the hind

METHODS OF PRODUCING HYPERTENSION

There are now many methods of producing hypertension in laboratory animals. In the account which follows these different methods will be considered separately, since it is unsafe to assume identity of mechanism until this has been demonstrated.

A. BY INTERFERING WITH THE KIDNEYS

RENAL ARTERY CONSTRICTION

The renal arteries may be constricted by three methods: by silver clips that can be screwed up or down to narrow the artery to the required size (Goldblatt and others, 1934), by silver clips previously made to the desired size (Pickering and Prinzmetal, 1938b), or by tying a ligature around the artery and a stylet, the stylet later being withdrawn (Drury, 1938).

Constriction of one renal artery, the other kidney being intact, produces either no hypertension, or a small rise of arterial pressure that lasts a few days to a few weeks only, in the dog (Goldblatt and others, 1934) and the rabbit (Pickering and Prinzmetal, 1938b; Daniel Prichard and Ward-McQuaid, 1954b). Constriction of both renal arteries produces a greater rise of pressure that tends to persist. An equally great effect is produced by constriction of one renal artery after excising the other kidney. Sometimes in such animals the arterial pressure starts to decline again and may be restored by severing the collateral vessels that have grown into the kidney from the pericapsular tissues and elsewhere (Cerqua and Samaan, 1939). In the dog, hypertension has been shown to persist for several years after renal artery constriction. Most of the dogs remained well, and many showed normal blood ureas and urea clearances (Fig. 5.2); but if the

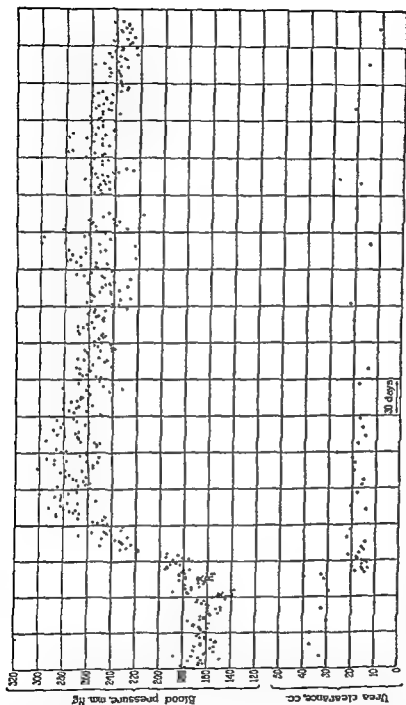


FIG. 5.2 Shows the production of prolonged hypertension by constricting both renal arteries in the dog. In this animal, it will be noted that the rise of arterial pressure took, approximately, sixty days to reach the plateau. The urea clearance was reduced to about half of its previous value (Goldblatt, Lynch, Hanzel and Summerville, (1934) *J. exp. Med.*, 59, 347). This is one of the most spectacular of the records in this classical paper, and left no doubt as to the significance of the hypertension. The slow rise of pressure may have been in part due to the atrophy of one and the hypertrophy of the other kidney—a usual result in the rabbit and, according to Govaert's, also in the dog, of constricting both renal arteries.

constriction was severe, the rise of blood pressure was greater, renal function impaired and the dogs would die of uræmia. One notable finding in most of Goldblatt's dogs was the gradual rise of pressure over periods of the order of one or two months, before the plateau was reached (Fig. 5.2). A similar observation was made on rabbits (Fig. 5.3) (Pickering and Prinzmetal, 1938b). On the other hand, in

Verney and Vogt's (1938) dogs, the pressure rose rapidly for the first four or five days, and thereafter was stable; occasionally, it fell later and could be restored by severing the collateral vessels around the kidney. Neither Verney and Vogt nor Pickering and Prinzmetal observed a rise of blood pressure from completely occluding one renal artery. Later Verney and Vogt (1943) studied the effects of renal artery compression on blood pressure and urine flow in the conscious dog in which, at previous aseptic operation, a Perspex box had been placed around the renal artery so that the small balloon it carried

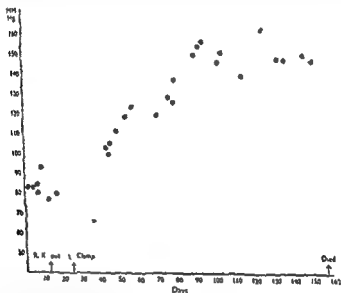


FIG 5-3 Shows the progressive development of hypertension after removing the renal artery. Acute arterial hypertension of this animal but not of the control (Clin. Sci., 3, 357)

would, when inflated, compress the artery against the side of the box. They showed that total occlusion, lasting two to 600 seconds, stopped urine flow, but produced no hypertension in most dogs. In some dogs, hypertension developed after occlusion for 10 to 20 minutes, but the hypertension disappeared after release of the artery. In some dogs, hypertension developed twenty minutes to two hours after release.

Unlike the rabbit and dog, the rat responds to constriction of only one renal artery, the other kidney being intact, with a prolonged and severe hypertension (Wilson and Byrom, 1939). Hypertension has also been produced in the monkey (macaque) by clamping both renal

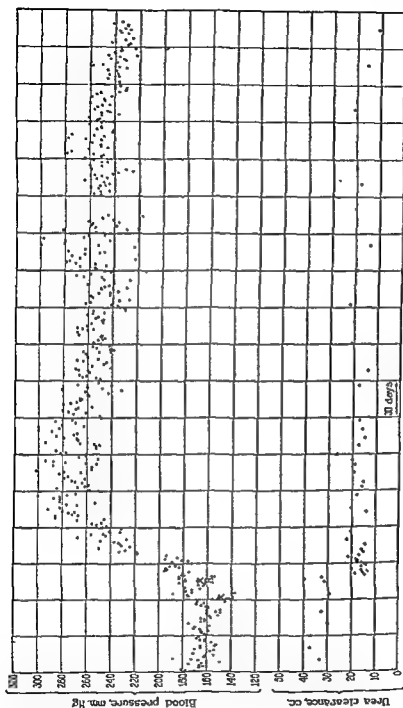


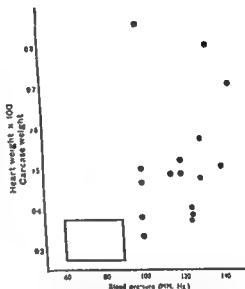
Fig. 5.2. Shows the production of prolonged hypertension by constricting both renal arteries in the dog. In this animal, it will be noted that the rise of arterial pressure took, approximately, sixty days to reach the plateau. The urea clearance was reduced to about half of its previous value (Goldblatt, Lynch, Hanzal and Summerville, (1934) *J. exp. Med.*, 59, 347). This is one of the most spectacular of the records in this classical paper, and left no doubt as to the significance of the hypertension. The slow rise of pressure may have been in part due to the atrophy of one and the hypertrophy of the other kidney—a usual result in the rabbit and, according to Govaerts, also in the dog, of constricting both renal arteries.

constriction was severe, the rise of blood pressure was greater, renal function impaired and the dogs would die of uræmia. One notable finding in most of Goldblatt's dogs was the gradual rise of pressure over periods of the order of one or two months, before the plateau was reached (Fig. 5.2). A similar observation was made on rabbits (Fig. 5.3) (Pickering and Prinzmetal, 1938b). On the other hand, in

kidney, the clamped kidney often shows tubular atrophy. The unclamped, and later the clamped, kidney may show arteriolar necroses and their consequences (Wilson and Byrom, 1939).

Heart. Cardiac hypertrophy, affecting the left ventricle chiefly or exclusively, has been demonstrated in the dog, rabbit and rat (Fig. 5.4). The degree of hypertrophy is approximately proportional to the height of the blood pressure (Fig. 5.5).

FIG 5.5 The relationship between blood pressure and the ratio $\frac{\text{heart weight} \times 100}{\text{carcass weight}}$ in rabbits with hypertension for one month or more. The rectangle represents the normal range (Pickering and Prinzmetal, (1938) *Clin. Sci.*, 3, 357).



Arteries In the vessels two kinds of lesions have been described. Goldblatt (1938a) and Child (1938) have described medial hypertrophy in the medium sized and small arteries from many parts of the body in dogs in which hypertension had been present for a long period. This is very similar to the findings in chronic hypertension in man (Chapter 11)

Arteriolar Necroses

Much more important are the acute arteriolar lesions which resemble exactly those of malignant hypertension in man. The lesions are of two chief kinds. In the acute necrotic lesions a mass of granular material appears in the arteriolar wall either in the intima, the media, or both and grossly narrows the lumen. In the later stages a cellular intimal thickening may represent the healing and organization of the "fibrinoid" lesions. These changes are more fully discussed in Chapter 11. These were described separately in 1938 by Goldblatt, by Child, and by Wilson and Pickering. Goldblatt found these lesions in dogs in which the renal arteries had been severely constricted, in

arteries, the systolic and diastolic pressures remaining elevated for sixteen months in one animal before it died of infection (Goldblatt, 1937b).

Anatomical Findings

Kidney. When the renal artery constriction is too severe the kidney is found infarcted *post mortem*, even though injection studies show that blood flow need not have entirely ceased (Pickering and Prinzmetal, 1938b). In the rabbit (Pickering and Prinzmetal) and dog (Govaerts, Verniory and Lebrun, 1950), atrophy of the clamped kidney is found if the other kidney is intact, or of one of the two kidneys if both renal arteries are clamped. When one kidney has been removed or has atrophied, the other is usually hypertrophied. When the kidney is neither hypertrophied nor atrophied, it looks remarkably normal macroscopically in dog and rabbit; in both species little abnormal is found on histological investigation. Goormaghtigh (1944) has observed enlargement, division and increased granularity of the juxtaglomerular cells which he believes to be secretory in function; this hypertrophy is pronounced in the first week following renal artery constriction, but later subsides until the cells have almost regained their former appearances by the nineteenth month.

In the rat, when hypertension is produced by clamping only one

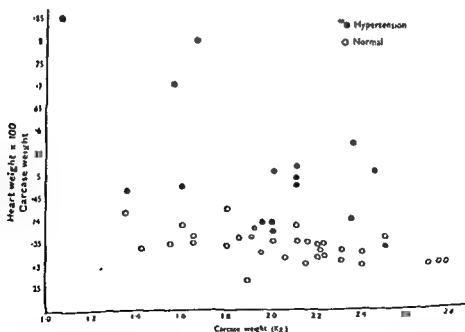
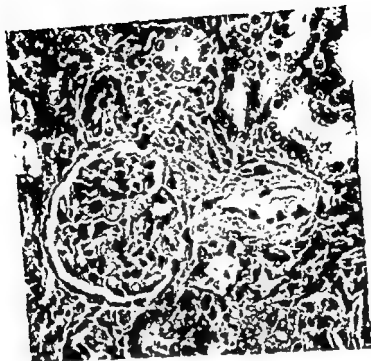


FIG. 54. The relationship between carcass weight and the ratio $\frac{\text{heart weight} \times 100}{\text{carcass weight}}$ in normal rabbits (open circles) and rabbits with hypertension from renal artery constriction (black discs) (Pickering and Prinzmetal, (1938) *Clin. Sci.*, 3, 357).



(a)



(b)

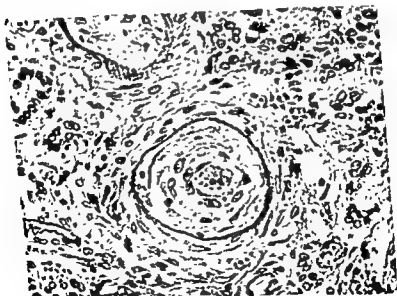
FIG. 5 & 6. Acute necrosis of afferent arterioles to glomerulus. (a) Above—rat kidney. Section made from intact kidney after severe hypertension had been induced by constricting the renal artery to the other kidney. (b) below—human kidney, malignant hypertension (Wilson and Byrom, 1970; *Lancet*, 1961).

which the arterial pressure had risen to high levels and in which renal failure had occurred. The lesions were found in the same sized arteries and arterioles and with the same distribution as in malignant hypertension in man, except for their significant absence from the kidney. Goldblatt did not find these lesions in animals in which renal function had remained good, even though some of them had had an equally high pressure, and he supposed that two factors were necessary, gross hypertension and renal failure. Child describes the anatomical findings in 18 dogs. He found the lesions of malignant hypertension in one dog in which hypertension had lasted eight months and the arterial pressure had exceeded 300 mm. Hg in the last two months. At no time was the blood urea nitrogen above normal, being 17 mg. per 100 ml. on the day the animal was killed. Wilson and Pickering described similar lesions with a similar distribution in the rabbit. They also noted the sparing of the kidney and, finding the lesions confined to those animals in which the rise of arterial pressure had been greatest, they suggested that the chief factor in producing the lesions was the level of intra-arterial pressure; the sparing of the kidney was attributed to the clamp on the renal artery having prevented the full rise of arterial pressure from being transmitted to the arteries in the kidney. The crucial experiment could not be done on the rabbit, since severe hypertension can only be produced in this species by constricting both renal arteries or by constricting one, after removing the other kidney. It was done by Wilson and Byrom (1939) who showed that a severe and persistent hypertension can be produced in the rat by constricting only one renal artery, the other kidney being intact. Arteriolar necroses had the same distribution as in dog and rabbit, with the important exception that they were also present in the unclamped, though not in the clamped, kidney in the early stages. Later on they occurred in the clamped kidney, though less severely. Figs. 5.6, 5.7 and 5.8 reproduce figures in which they illustrated the identity of the lesions in the experimental animal and in man, a conclusion whose importance needs no emphasis. Wilson and Byrom concluded that the arterial lesions were due to hypertension. They found, however, no relationship between the presence or absence of arteriolar lesions and either the severity or duration of hypertension. They suggested that two factors were concerned in producing the lesions, namely, arterial pressure and vasoconstriction. Their pressures were, however, measured under anaesthesia, which has been stated to alter the pressure of hypertensive rats (Reed and others, 1944).

Arteriolar necroses have also been found in the rabbit with hypertension due to renal artery constriction by Fleming (1953) and Daniel, Prichard and Ward-McQuaid (1954c). Fleming found them in gut and brain of animals dying spontaneously of acute and, usually, gross

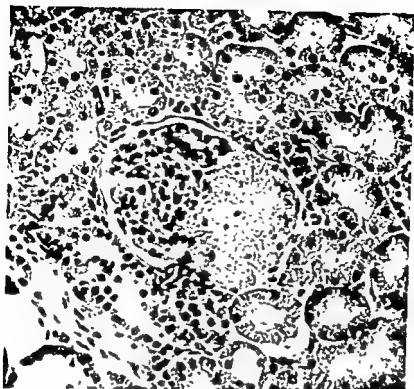


(a)

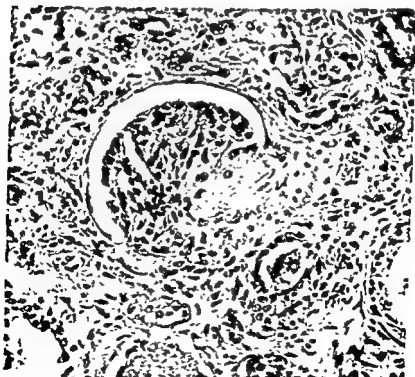


(b)

FIG. 5.8 Cellular thickening of intima of a medium-sized artery (end-arteritis fibrosa) (a) Above—rat kidney, (b) below—human kidney (Wilson and Byrom, (1939) *Lancet*, i, 136)



(a)



(b)

FIG 57. Acute focal glomerular necrosis (a) Above—rat kidney, (b) below—human kidney (Wilson and Byrom, (1939) *Lancet*, 1, 136)



(a)



(b)



(c)

FIG 5 9. Three photographs of the pial vessels of a rat taken through a transparent window of acrylic resin moulded to fit the cranial defect. (a) October 20th Simple hypertension; B.P. 170, artery and branches appear normal. (b) December 1st Early encephalopathy with excitability and muscular tremors. B.P. 230 Shows localized waist-like constrictions of the artery, one branch being barely visible, and slight distension secondary to spasm. (c) Three days after removing clamp from renal artery. B.P. 140. Vessels normal (Barnes, 1954; *Lancet*, ii, 901).



(a)



(b)



(c)

FIG. 5. 10. As Fig. 9. (a) October 26th. Simple hypertension, B.P. 170. arteries normal. (b) November 13th. Twenty minutes after onset generalized convulsions, B.P. 196, widespread uniform contraction of the cerebral arteries, especially the smaller branches, no distortion. (c) November 15th. Four days after removing clamp from renal artery, B.P. 118, arteries normal (Byrum, 1954, 7).

hypertension and uræmia. He did not find them in animals with more chronic and even higher pressures in which the clamped kidney had been finally removed and the animal died in uræmia. Daniel and others (1954c) observed several exceptions to the hypothesis that the lesions are attributable simply to the height of the arterial pressure. Further strong evidence for intravascular pressure as the causal factor was obtained by Byrom and Dodson (1948), who injected 2 ml. of warm saline quickly, ten or fifteen times, into the aorta of anesthetized rats and found lesions in the kidneys two days later. These

pressure has also been obtained in the dog by Goldblatt and co-workers (Goldblatt, 1948), who showed that when one renal artery was greatly constricted and the opposite ureter tied, the animals developed gross hypertension and uræmia, and after death showed arteriolar necroses in the kidney with ureter tied but not in that with artery constricted.

A very different explanation has been put forward by Winternitz and his colleagues (1940). They found that, in the dog, bilateral nephrectomy killed the animal without hypertension or vascular lesions. Bilateral ligation of the renal arteries or of the ureters produced hypertension and necrosis of muscle "including heart muscle, smooth muscle of blood vessel walls, hollow viscera and diaphragmatic muscle". Thinking that a renal substance might be responsible for these tissue lesions, they showed that injection of stored saline extracts of necrotic and fresh dog's kidney produced a profound fall, followed by a prolonged rise, of pressure in nephrectomized dogs, the same lesions being found at post-mortem examination as after ureteric or renal artery ligation. Working with hog renin, they were unable to separate the pressor fraction from that producing the tissue injury. Experiments differing in detail but with a similar meaning were published by Leiter and Eichelberger (1942, 1943). They injected hog renin into dogs which developed a foreign protein reaction. In 15 dogs with experimental renal lesions, death occurred within a few days of the injection, and in 12 of these, the arterioles showed a hyaline degeneration and fibrinoid necrosis with leukocyte emigration and hemorrhage; in four of these dogs there was not sufficient renal damage nor severe enough hypertension to account for the lesions.

These experiments are open to two very serious criticisms, so far as our present problem is concerned. In the first place, hog renin is known to be antigenic in the dog, and Rich and Gregory (1943) have shown that the injection of foreign protein produces widespread arterial lesions, in which fibrinoid necrosis is a prominent constituent, though the whole picture is akin to that of polyarteritis nodosa. In the second place, none of these extracts were prepared under aseptic

precautions, nor were they sterilized before use. It is a well-known trap in the case of the dog, that the tissues contain *Clostridium welchii* even when excised aseptically. Experiments from my laboratory have shown that intravenous infusions of rabbit renin into rabbits produce death with widespread hæmorrhage, unless extreme care is taken to sterilize the extracts and to work under strict aseptic conditions. With strict asepsis, infusions of rabbit renin into rabbits produce hypertension that is maintained for the duration of the infusion (up to eighteen days) (Blacket, Depoorter and others, 1950). In such animals acute arteriolar necroses were not found, except mildly in two animals in which the level of arterial pressure had been previously raised by subtotal nephrectomy (Pugh, Pickering and Blacket, 1952). Surveying these animals, together with those earlier reported in which hypertension had been produced by renal artery constriction, it seemed, from our experiments in the rabbit, that the chief factor determining arterial necrosis was the level of arterial pressure actually attained. That a renal substance is unnecessary for the production of these lesions is finally demonstrated by their occurrence in animals with hypertension following bilateral nephrectomy, in which the animals are kept alive by dialysis (Muirhead and others, 1949) or by parabiosis (Ledingham, 1951).

Byrom's (1954) beautiful and careful experiments on hypertensive encephalopathy in the rat have thrown further light on the mechanism by which arteriolar necrosis is produced. He produced hypertension by constricting one renal artery, the other kidney having been removed. Fits occurred in animals with the highest arterial pressures and were frequently preceded, as in man, by a further rise. The fits were not affected by bilateral section of the cervical sympathetic nerves, but were promptly abolished by removing the renal artery clamp, which procedure reduced the blood pressure at any stage of the hypertension. Histologically, arteriolar necroses were common in the brains of affected animals, as were infarcts and hæmorrhages; but any or all of these might be absent. The affected brains were oedematous and the oedema was especially marked in areas showing capillary damage and which were stained blue after intravascular injection of trypan blue before death. To explore further these vascular changes, Byrom prepared windows of acrylic resin, specially moulded to fit the brain without distortion, and observed and photographed the pial vessels before and during hypertensive encephalopathy, and after abolishing the hypertension by removing the clamp. In simple hypertension without encephalopathy, the arteries appeared normal, or slightly and uniformly narrowed. Of 13 rats in which the surface of the brain was not distorted by the window, spasm of the cerebral arteries and arterioles was seen during the fits in 12, and absent in only one. In

encephalopathy, the larger arteries frequently showed localized constrictions (Fig. 5.9), while the smaller arteries and arterioles showed generalized or localized narrowings (Fig. 5.10), and the brain substance appeared pale. These arterial constrictions invariably went when the pressure was reduced by removing the clamp. Localized arterial spasm was also observed in the exposed intestine, and the more frequently the higher the pressure. Byrom attributes this arterial spasm to the grossly raised intravascular pressure, recalling Bayliss's (1902) experiments suggesting that an increase in intra-arterial tension produces, by a direct action on the muscle fibres of the arterial wall, an increase in their tension. This arterial spasm leads to tissue anoxia, to tissue oedema and to arteriolar necrosis in those regions where it occurs. Hypertensive encephalopathy is thus the result of ischaemia of the brain consequent on the arterial spasm provoked by the grossly raised intra-arterial pressure. Fibrinoid necrosis of the wall is the local result, on the small artery or arteriole, of its powerful contraction evoked by the gross rise of intravascular pressure. In postulating arterial spasm as a necessary intermediate step between high intravascular pressure and arteriolar necrosis, Byrom is much influenced by his early observations (1937) in which he found that vasopressin produced intense focal blanching of the kidney with subsequent oedema, or infarction, and arterial and arteriolar necrosis in the affected areas.

It is still unknown whether the "fibrinoid" material in the walls of the arterioles and small arteries represents a disintegration of the tissues of the wall, or whether it represents blood proteins which have permeated there, for the latter view may be cited the great expansion of wall at the expense of lumen and the frequent presence of red-cells, mixed with the fibrinoid, and sometimes separating the muscle fibres of the media. A further difficulty in unravelling the causation of these acute arteriolar necroses is that rather similar lesions may be produced in other ways. The lesions resembling polyarteritis nodosa already cited and produced by horse serum are rather more inflammatory in nature; similar lesions occur in tuberculous meningitis (Daniel, personal communication), and in the edges of infarcts. It is possible that there is more than one type of lesion designated as fibrinoid necrosis.

Atheroma In the dog, rabbit and rat, atheromatous lesions of the aorta and large arteries are unusual. But if an atheroma producing dist is given, the lesions are more widespread and severe in animals which have hypertension produced by renal artery constriction (see Chapter 11)

The Nature of the Renal Change Producing Hypertension

Nature of Disturbance in Kidney

Since the paper of Goldblatt and others (1934), entitled "Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia," it has been customary to refer to the affected kidney as the ischemic kidney, and to assume that the disturbance within the kidney which initiates the hypertension is a diminution in blood flow. That a conspicuous narrowing of the main arterial channel would reduce blood flow was a very natural assumption, and was supported by the measurements of Levy, Light and Blalock (1938), who found a 40 per cent. decrease in flow in hypertensive animals seventy-three days after constricting the renal artery. There are, however, a number of experiments suggesting that the kidney has considerable powers of maintaining its rate of blood flow, despite changes in the pressure of blood supplying it (Forster and Macs, 1947). Corcoran and Page (1942a) found that, in dogs, the clearances of phenol red and inulin were essentially unaltered when hypertension developed after clamping the renal artery. Alpert and Thomas (1940) concluded from clearance observations that the renal blood flow may remain unaltered in hypertensive animals. Enger, Linder and Sarre (1938), Warthin and Thomas (1943) and Schroeder and Steele (1940) have also found that, after constricting the renal artery, the blood flow through the kidney may quickly return to its previous level unless the constriction is extreme.

Clamping the renal artery may also be expected to produce a fall in arterial pressure distal to the clamp. Mason, Robinson and Blalock (1940) punctured the artery of the explanted right kidney distal to the clamp in unanesthetized dogs. They found that in 14 out of 15 hypertensive dogs the pressure in the artery distal to the clamp was less than before the constriction, and was always considerably less than femoral artery pressure, to which, in the hypertensive animal, it was not directly related.

The most recent experiments on this subject are those of Daniel, Prichard and Ward-McQuaid (1954c, d). They have confirmed the pressure fall across the clamp, but found a drop of 22 mm. Hg in a dog whose systemic arterial pressure had returned to normal by the time the observations were made. In rabbits they found that the fall of pressure across the clip was less than the degree of hypertension in the aorta. In both species they observed three kinds of change in angiograms obtained by injecting thorotrast into the renal artery through a catheter introduced via the femoral artery. Immediately after applying the clip, the renal circulation was reduced. Later, those animals which showed a sustained hypertension without renal

failure had normal angiograms; animals with gross renal failure showed a reduced circulation throughout the kidney, particularly in the more peripheral zones.

Finally, it has been suggested by Corcoran and Page (1942a) that diminution in pulse pressure is the effective stimulus, citing in support experiments on the perfused kidney in which reduction in pulse pressure leads to a development by the effluent blood of a vasoconstrictor action on the perfused rabbit's ear (Kohlstaedt and Page, 1940). Perfusion of the rabbit's ear as a method of detecting renin in the blood has, however, been severely criticized by Landis and others (1943), who have pointed out the numerous uncertainties in the method.

As was mentioned earlier, constriction of one renal artery, the other kidney being intact, produces only a small and transient rise of pressure in the dog and rabbit. In the rabbit, the kidney whose artery has been constricted atrophies, the other hypertrophies (Pickering and Prinzmetal, 1938b), and this is probably true also of the dog (Govaerts, Verniory and Lebrun, 1950). The reduction in blood flow to a kidney has been accompanied presumably by a decrease in work, which has been transferred to its fellow. When this is prevented by removal of the other kidney, a more severe and prolonged hypertension ensues. This, it would seem, is the most natural explanation of the protective action of the normal kidney which has been very fully discussed (see

herefore, it
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produced by feeding salt, urea or meat noted by Verney and Vogt (1938), Cash and Wood (1938) and MacLachlan and Taylor (1940); these effects were, however, not found by Grollman, Harrison and Williams (1940), Philipshorn, Katz and Rodbard (1941) and Goldblatt et al. (1942).

ren

oth

Blum showed in hypertensive dogs with a 40 per cent reduction in renal blood flow, that the renal arteriovenous oxygen difference was not reduced, presumably, therefore, the oxygen consumption was reduced to a similar degree. It is clear that a change in oxygen consumption of this order must be accompanied by profound metabolic changes in the kidney, some of which may be responsible for hypertension. As yet there is no clear indication what these changes are, if any.

As has been pointed out in Chapter 4, the stimulus to the release

of renin from the kidney appears to be either a reduction in renal arterial pressure or blood flow, but not anoxaemia or tissue anoxia. It has been shown (Steiner, Weeks and Barach, 1940) that hypertension due to renal artery constriction is not affected by inhaling 100 per cent. oxygen (which would not increase oxygen supply to the kidney very much) for forty-eight hours; nor did inhalation of 7 to 10 per cent. O_2 raise the arterial pressure more than in normal dogs.

The reader will be left in some confusion as to the nature of the change in the kidney which induces hypertension. It would seem that in the early stages after renal artery constriction, there must be a reduction in arterial pressure and renal blood flow; later these may be counteracted by the rise in systemic pressure and by local vascular changes in the kidney. A change in the metabolism may also occur. At the present time it seems that our methods for investigating such questions are too crude to give a clear answer.

The Mechanism of Hypertension following Renal Artery Constriction

The Pattern of the Circulation

To gross inspection, the skin circulation differs in no way from normal in the rabbit with hypertension; the ears paling and flushing with changes in body temperature; and constricting to sensory stimuli which also raise arterial pressure. The denervated ear is paler and cooler than its flushed fellow, and the differences between them are not exaggerated by the supervention of renal hypertension (Pickering and Prinzmetal, 1938b); if a pressor substance is concerned it is not one to which the denervated ear is unduly sensitive.

In the dog, cardiac output is normal (Holman and Page, 1933) and there is no reason to suspect an alteration in blood viscosity. The rise of blood pressure, therefore, is due to vasoconstriction. From the appearance of the rabbit's ear, it may be inferred that the constriction affects predominantly the small arteries and arterioles and that it is more or less uniformly distributed over the body. This, however, is conjecture and has never been put to the test of measurement.

Since the pulmonary artery pressure is normal (Katz and Steinitz, 1940), the vasoconstriction probably spares the lungs, a conclusion supported by the absence of right ventricular hypertrophy.

Evidence for a Humoral Mechanism

There is no doubt that the hypertension can be produced through non-nervous mechanisms. If the kidney is grafted into the neck or thigh, constricting the artery produces hypertension that is abolished by removing the clip (Blalock and Levy, 1937; Glenn, Child and Heuer, 1937). When the sympathetic chains have been completely extirpated

preparation. The vasoconstrictor action of plasma obtained from renal vein blood of dogs with hypertension was significantly greater than plasma similarly obtained from dogs without hypertension (Fig. 5.11).

Braun-Menendez, Fasciolo, Leloir and Muñoz (1939) showed that the pressor substance present in the renal vein blood, after recent constriction of the renal arteries, was soluble in 75 per cent. acetone, was thermostable and dialysable. They named this substance hypertensin, and they later showed that a substance having similar properties was formed by the action of renin on plasma proteins. Renin and hypertensin are fully discussed in Chapter 4, page 69 *et seq.*

Dell'Oro and Braun-Menendez (1942) assayed the blood of the dog for renin using the direct method of Leloir and others (1940). They obtained blood from the renal vein of a kidney explanted underneath the skin of the flank and from the femoral artery. In a normal dog no renin was demonstrable in blood from either source. The renal artery was clamped. One or two days later, when the pressure of the dog had risen by 20-40 mm. Hg, between 0.8 and 1.2 units of renin per 12 ml. were found in renal vein blood, rather less in femoral artery blood. Intravenous infusion of renin for thirty to forty minutes at a rate giving a similar rise of pressure produced rather smaller amounts of renin in femoral artery blood. When the pressure returned to normal after stopping the infusion no renin was found in the femoral artery blood.

These experiments seemed to establish that the hypertension following renal artery constriction was due to an outpouring of renin into the renal vein, the renin reacting with hypertensinogen to produce hypertensin and thus causing a generalized vasoconstriction. It is to be noted, however, that these experiments refer to the period shortly following renal artery constriction. Similar assays made in dogs with hypertension of three months' to four years' duration by the Buenos Aires workers *have failed to demonstrate renin in the renal vein blood* (Braun-Menendez and others, 1946). Haynes and Dexter's (1947) results were essentially similar. Pickering, Prinzmetal and Kelsall (1942) were unable to recover renin from the blood of rabbits with chronic hypertension though they could demonstrate the presence of renin in the blood ten minutes after its intravenous injection. Thus this mode of enquiry fails to establish that the later stages of hypertension are also due to the outpouring of renin. Govaerts and Verniory (1949) criticized previous work because the methods used to obtain renal vein blood were often such as to interfere with renal blood flow, and thus stimulate secretion of renin. Using a catheter introduced via the femoral vein in trained conscious dogs, they were unable to detect any vasoconstrictor substance in the renal vein blood in dogs with

hypertension of some months' duration, though a weak vasoconstrictor effect was usually obtained in blood removed three to thirty-one days after constricting the renal arteries. This vasoconstrictor effect was not due to adrenaline or noradrenaline, and differed in some respects from that of renin (Govaerts and Verniory, 1952). Govaerts' criticism that the methods used to obtain blood may themselves cause the release of renin are also applicable to contemporary and later work. Thus Gollan, Richardson and Goldblatt (1948) obtained blood from jugular vein or carotid artery into a chilled receiver and, after incubating it at 0° C. for twenty-four hours, coagulated it by heat and injected the supernatant into trained unanæsthetized dogs. They obtained no rise of blood pressure with 200 ml. blood from normal dogs and small and irregular responses with the same quantity from hypertensive animals; larger quantities yielded pressor activity but so did larger amounts from normal animals. When 200 ml. lots were withdrawn, pooled, extracted and tested, injections equivalent to larger amounts of blood from normal dogs gave no pressor activity, whereas those from hypertensive dogs did. Similarly, Skeggs, Kahn and Shumway (1951) dialysed the blood of hypertensive dogs against 500 ml. Ringer solution in an artificial kidney, and extracted the dialysate by a method which gave a 50 to 80 per cent. recovery of hypertensin. They concluded that "Hypertensin was obtained in significantly larger amounts from the animals in the early phases of experimental renal hypertension than in those with long continued elevation of their blood pressure or in normal dogs." They could not, however, rule out the possibility that the procedure itself was sufficient to cause the kidneys to secrete renin.

At the same time as these experiments were being performed, evidence of a different kind and from a different species, the rabbit, was accumulating to suggest that the renin hypothesis was not a sufficient explanation for this type of hypertension.

The first publication throwing doubt on the renin hypothesis was that of Taggart and Drury (1940), who showed that, when enough renin was given to produce tachyphylactic extinction of the pressor response to intravenous injection, the level of arterial pressure in a hypertensive animal was unchanged. They argued that since hypertension persisted while the vascular system had ceased to respond to renin, the hypertension could not be due to that substance. These experiments were carried out in rabbits with hypertension of long duration—but were repeated by Drury and others (1951) with similar results in hypertension of short duration. Prinzmetal and I had begun in 1936 the assay of renin in kidneys of rabbits with ————
and hypertension ————

able variation, being greater in young rabbits than in old, but otherwise not related to factors that we were able to control. In a given rabbit, the two kidneys had equal renin contents within the limits of error of our method. In animals from which one kidney had been removed, it was found that (1) in animals with hypertension of up to eight days' duration, the kidney not being infarcted, the renin content of the kidney was increased; while (2) in animals with hypertension of over two months' duration the renin content of the kidney was normal (Fig. 5.12). We were able to confirm these results by comparison of

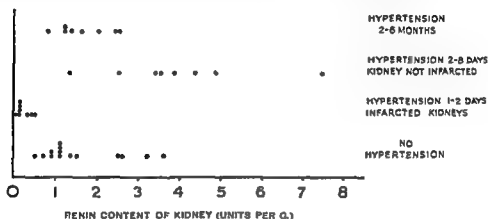


FIG. 5.12. Shows the renin content of kidneys in a series of rabbits with one

the clamped kidney with the previously excised normal kidney in the same animal. While the renin content of the kidney does not provide unequivocal information as to the rate of secretion of renin, these results suggested that the rate of formation of renin during the first week of hypertension might be increased, while after two months it might have returned to normal. Another chance observation led to a similar conclusion. It was found that in animals in which one kidney had been removed and hypertension produced by clamping the other renal artery, excising the ischaemic kidney after four to eight days restored the arterial pressure to normal in less than twenty-four hours in seven out of eight animals (Fig. 5.13); while excising the ischaemic kidney after two months left the hypertension unaltered during the three days the animals survived in all of eight rabbits (Fig. 5.14) (Pickering, 1945). The difference in behaviour could not be attributed to alterations in a contralateral and previously normal kidney for that kidney had been removed. Nor could it be attributed to arteriolar necrosis, for none was found; nor to progres-

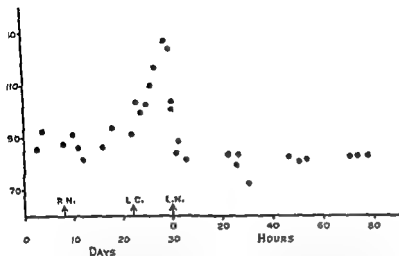


FIG. 5. Rabbit, right kidney removed (R.N.), left renal artery constricted and kidney made subcutaneous (L.C.), and eight days later removed (L.N.). Arterial pressure remains there (945), *Clin. Sci.*.

(J. end)

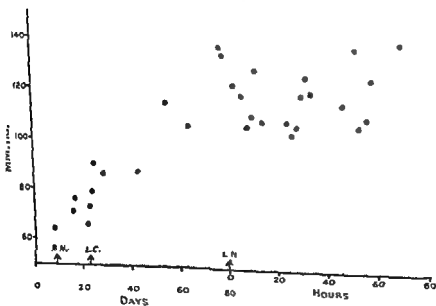


FIG. 6. Rabbit with right kidney removed (R.N.), left renal artery constricted (L.C.), and kidney made subcutaneous (L.N.). Arterial pressure remains there (945), *Clin. Sci.*.

sive renal failure, for blood levels of urea before nephrectomy were normal. The response to renin was increased in rabbits with chronic hypertension and was further increased by nephrectomy. The rabbit with chronic hypertension is, after nephrectomy, exquisitely sensitive

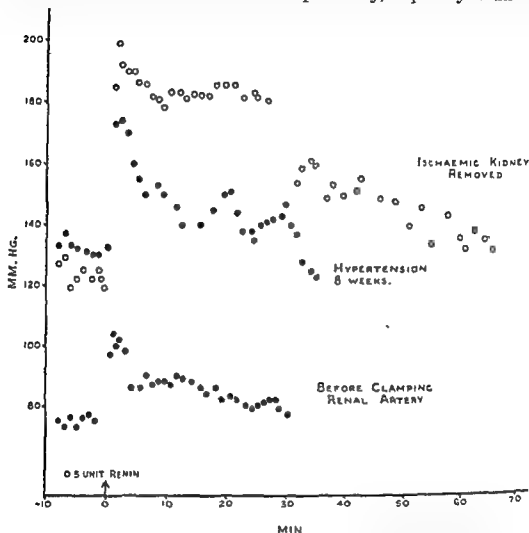


FIG. 5.15. Rabbit as in Fig 5.14. Right kidney removed July 28th, 1943. Shows the responses to 0.5 unit renin (a) on August 5th, 1943, before two months after 1943, forty-eight response of the ring (1945), Clin.

Sci., 5, 229).

to injected renin (Fig. 5.15) Nevertheless, the response to a single intravenous injection does subside in about four hours, while the pre-existing hypertension is not essentially altered at any time after removing the ischaemic kidney. It therefore seemed extremely probable that, at this stage, the hypertension was not due to renin; and it seemed, in fact, that the hypertension was sustained by a non-renal

mechanism. In the rat, Byrom and Dodson (1949) showed that removal of the clamp from the sole ischemic kidney restored the arterial pressure. Blacket and Sellers (1951) showed that removing the clamp from the renal artery in the rabbit with chronic hypertension also abolishes the hypertension, though it does so rather slowly; and they, therefore, suggested that the mechanism later coming into play was ultimately dependent on a renal change.

Daniel, Prichard and Ward-McQuaid have recently repeated these experiments with important results. Producing hypertension by clamping the left renal artery after the right kidney had been excised, they showed that, in hypertension of some months' duration, hyper-

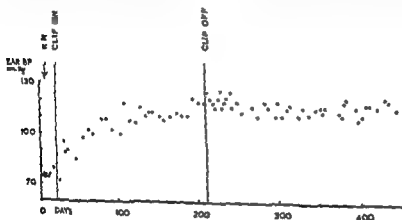


FIG 5 16 (Blacket and Sellers, 1951)

tension was not abolished by excising the kidney (Daniel, 1951).

In animals from which the clip has been removed and hypertension persisted, angiography revealed a bend but not a narrowing of the renal artery.

While it seems a pity that they did not clinch the argument by finally removing the kidney from animals similar to that of Fig 5 16, there is no evidence that the cause of the

final hypertension lies in the kidney. The vicious circle postulated by Volhard (1931) and by Wilson and Byrom (1941) is clearly not here concerned. A change in the level, at which extrarenal homeostatic mechanisms are set, seems by far the most likely explanation, but has not yet been investigated. As we shall see, a study of human hypertension reveals an apparently similar phenomenon, namely the persistence of hypertension in some cases after removal of a unilaterally diseased kidney, a phaeochromocytoma or repair of a coarctation of the aorta (Chapters 17, 20 and 22). The observation that hypertension may persist when the sole ischaemic kidney is removed (Pickering, 1945) is in fact the first example of what appears to be a general phenomenon, namely, that blood pressure may remain high even though the abnormality originally responsible has been removed.

At the time when our observations on the effects of excising the ischaemic kidney in the rabbit were published, they seemed in conflict with the results on the dog, in which animal Goldblatt (1937b), Verney and Vogt (1938) had found that excising the kidney whose renal artery had been constricted, the other kidney being intact, abolished the hypertension, and Rodbard and Katz (1939) had observed this with the sole remaining kidney. Subsequent workers have, however, found that excising the sole ischaemic kidney in dogs with chronic hypertension does not abolish it (Shipley, Helmer and Kohlstaedt, 1947; Oppenheimer, Rosenak and Oppenheimer, 1952; Govaerts, Verniory and Lebrun, 1950).

In the rat, Wilson and Byrom (1941) found that when hypertension had been produced by clamping one kidney, the other being intact, if the clamped kidney was removed, the arterial pressure might fall to normal, or remain unchanged or rise to higher levels. From histological examination of the unclamped kidney, they concluded that when it contained few or no arteriolar lesions, the arterial pressure fell to normal when the clamped kidney was removed; but when arteriolar lesions were pronounced in the unclamped kidney, hypertension persisted or was enhanced when the clamped kidney was excised. They were thus led to the concept, which Volhard had previously put forward, of a vicious circle in Bright's disease; of a hypertension which, when severe enough, led to renal ischaemia, the renal changes leading to a release of a pressor substance with further accentuation of the hypertension. Friedman, Jarman and Klemperer (1941) produced hypertension by wrapping one kidney in cellophane which produced perinephritis (see page 113). When this kidney was removed the hypertension usually persisted though vascular lesions were not always found in the other kidney or elsewhere. Patton, Page and Ogden (1943) found residual hypertension to be related to the duration of the preceding hypertension and likewise related it to arteriolar

changes in the opposite kidney. Later Ogden and his colleagues (Reed and others, 1944) found that nembutal and yohimbine were without influence on a recent, but abolished a long-standing, hypertension and thought this was evidence of a change from a humoral to a nervous mechanism. However, the effects of anaesthesia are, in general, very variable in hypertensive animals and are not quite as closely related to the phase of hypertension, at least in the rabbit, as those authors found in the rat. Floyer (1951) confirmed Wilson and Byrom's findings about the relationship between the persistence of hypertension and the presence of arteriolar lesions in the remaining untouched kidney. He also showed that, when hypertension had been produced by clamping one renal artery the other kidney having been removed, excising the ischaemic kidney was not followed by any fall of arterial pressure, whether the hypertension was of short (seven to ten days), or of long (up to forty-six weeks), duration. In fact, there is no evidence whatsoever that, in the rat, renin is concerned in the mechanism of hypertension following renal artery constriction.

Removal of the clip from the renal artery in the rat with hypertension of twelve weeks' duration was found by Byrom and Dodson (1949) to restore the arterial pressure to normal in twelve hours; they, therefore, concluded that a renal mechanism was responsible. When the clip is removed from one renal artery, the other kidney being intact, whether or not the hypertension persists depends on the presence or absence of arteriolar lesions in the opposite kidney (Floyer, 1951).

Antirenin is a substance produced by the injection of heterologous renin (e.g. hog renin into dogs). It neutralizes the effect of renin added to plasma containing it. Wakerlin and Johnson (1941) reported, and Goldblatt (1947) confirmed, that the production of antirenin abolishes an existing, and prevents an expected, hypertension from renal artery constriction. Goldblatt (1947) reviews this controversial subject.

The Effects of Infusing Renin and Other Substances Intravenously

The possibility that the release of renin into the renal vein is concerned in the production of hypertension following renal artery constriction can be approached in another way. Can hypertension be produced by infusing renin into a vein in the conscious animal and has this hypertension the properties of that due to renal artery constriction? To many workers it has seemed that since the response to renin can be extinguished by repeated injection, renin is unlikely to be the cause of renal hypertension. Page (1939a) failed to produce a sustained hypertension in the anesthetized dog by continued intravenous infusion of renin. On the other hand, Hill and Pickering (1939) found

that small doses of rabbit renin infused into the ear veins of conscious rabbits for four hours would produce a sustained hypertension of about 30 mm. Hg; the arterial pressure returned to normal about four hours after stopping the infusion. With larger doses, hypertension was not sustained. Taggart and Drury (1940) obtained similar results. However, in view of the doubt concerning the rôle of renin and the probability that it is concerned in the early stages, but is later displaced by another mechanism which might conceivably be initiated by renin secretion, it seemed of great importance to extend these observations

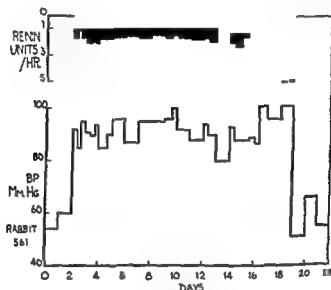


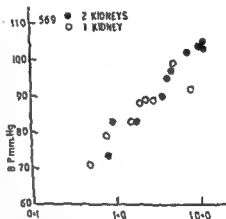
FIG. 5.17. Shows the average daily arterial pressure in rabbit 561. On days 1 and 2 saline was infused, on days 3-19 a preparation of rabbit renin was infused and on days 20-22 saline was again infused via the internal jugular vein. During the first part of the infusion the dose was kept fairly constant and the hypertension shows no tendency to increase or decrease; during the later part of the infusion the dose was increased (Blacket, Depoorter, Pickering, Sellers and Wilson (1950), *Clin. Sci.*, 9, 223).

for much longer times. When full aseptic precautions were taken, Blacket and others (1950) showed that it was possible to produce a sustained hypertension by infusing a partially purified preparation of rabbit renin into rabbits for as long as eighteen days. When the dose of renin was kept constant, the degree of hypertension also tended to remain constant, at least for periods of the order of ten days (Fig. 5.17). When the dose of renin was increased, equal increments in dose produced progressively smaller increases in the degree of hypertension. With the highest rates of dosage tested (16 units renin per hour), the degree of hypertension tended to fall, and the response to injected renin to be suppressed. The relationship between the degree of hypertension and the logarithm of the dose was approximately

linear (Fig. 5.18) and was not appreciably altered by removing one kidney and a third of the other. When the infusion was stopped the arterial pressure fell to its original level, or below, in times varying from one and a half to over five hours. The animals receiving renin

rate. At post-mortem, there were some changes in lungs, kidneys and elsewhere due to embolism, and the heart was hypertrophied. Arteriolar necroses were found only in two animals in which the level of arterial pressure had been raised by removal of one and one-third kidneys

FIG. 5.18 Rabbit 569. Shows the relationship between the average arterial pressure during the relevant periods of the infusion and the rate at which renin was infused, the latter plotted on a logarithmic scale. The open circles relate to the first infusion of renin which lasted eleven days, after which one kidney was removed, and after recovery, a second infusion of renin given lasting fifteen days. The response is approximately a linear function of log-dose and is not altered by removal of the kidney (Blacket, Depoorter, Pickering, Sellers and Wilson (1950), *Clin. Sci.*, 9, 223).



before the infusion, the lesions were not numerous and were confined to the gut (Pugh, Pickering and Blacket, 1952)

One further point that emerged in these experiments is relevant to our theme. As shown in Figs. 5.2 and 5.3, the arterial pressure after renal artery constriction does not reach its full height at once. Commonly it rises gradually over a period varying from two to six weeks. The severest hypertension that could be produced in the rabbit by infusing renin was of the order of 40 mm. Hg. In experiments in which hypertension was produced by excising one kidney and constricting the other renal artery, the maximum rise of blood pressure observed in the first two weeks was 40 mm. Hg; but of 22 rabbits with hypertension lasting two months or more, 13 had rises of more than 40 mm. Hg, the largest being 73 mm. Hg. Thus the hypertension that is produced in the first two weeks, by constricting the renal artery, can be matched by infusion of renin; that occurring later may be much greater (Blacket and others, 1950).

The pressor response to a single injection of renin was depressed

during the hypertension produced by renin infusion, slightly with small rates of infusion, greatly with large rates. This is in conformity with the dose response curve.

The quantity of renin necessary to produce a sustained hypertension, comparable to that observed in the first two weeks of renal artery constriction, was 4 units per hour, as compared with the total renin content of the kidneys of 32 units¹ found by Pickering, Prinzmetal and Kelsall (1942). To produce the order of hypertension observed the whole renin content of the kidney would thus need to be changed once every eight hours.

These experiments thus show that increased secretion of renin into the renal vein blood is, indeed, a perfectly possible basis for the humoral mechanism of this hypertension. It produces the same order of hypertension having the same gross characters. Hypertension is abolished in about the same time when a renin infusion is stopped or a sole ischæmic kidney removed. Unfortunately, the demands made on man and rabbit did not enable these infusions to be continued longer than eighteen days. That the arterial pressure showed no tendency to remain elevated when the infusion was stopped may have been due to the time being too short, the renin being impure, or the later mechanism being induced by some change other than increased renin secretion.

Influence of the Endocrine Glands

Hypophysectomy lowers the arterial pressure of the normal dog. In hypophysectomized animals, constriction of the renal arteries produces a rise of arterial pressure (Page and Sweet, 1937; Goldblatt and others, 1942). Ogden, Page and Anderson (1944) produced hypertension in rats by renal artery constriction and showed that removal of the neurohypophysis produced diabetes insipidus and no fall of pressure. Removal of the anterior lobe abolished the hypertension. It would seem, therefore, that the anterior lobe secretions are essential for the normal behaviour of the circulation. But even in its absence, a rise of blood pressure can be produced by renal ischæmia. More striking is the effect of adrenalectomy. In their original paper, Goldblatt and his colleagues (1934) had shown that the rise of arterial pressure due to renal artery constriction was not prevented by removing one adrenal and the medulla of the other. Goldblatt (1937a) showed that in the totally adrenalectomized dog, constriction of the renal arteries did not produce a rise of pressure, and that adrenalectomy abolished a

— Page and Sweet (1937a)

pre-existing hypertension in animals maintained on sodium salts but not cortical extract. These effects were confirmed by Blalock and Levy (1937). Goldblatt (1937a), Collins and Wood (1938) and Page (1938) showed that some rise of blood pressure could be obtained in such animals when cortical extracts were given in addition to sodium salts. Collins and Wood found that some hypertension persisted after adrenalectomy when substitution therapy was associated with a low serum Na and high serum K. They, therefore, thought that the effects of renal artery constriction and adrenalectomy were summative. Adrenalectomy has been reported by some authors to reduce the sensitivity to renin, which has been attributed to a reduction in the hypertensinogen content of the blood (for review see Braun-Menendez and others, 1946).

Removal of gonads, thyroid and pancreas does not interfere with hypertension due to renal artery constriction (for review see Goldblatt, 1947).

As will be seen later in this chapter, hypertension can be produced in some species by sodium chloride, or the salt hormone of the adrenal cortex or the two combined; further, adrenalectomy prevents the rise of pressure due to nephrectomy in the parabiotic rat. These facts, together with the enhanced hypertension found by some authors when salt is given (see p. 97), have suggested that an excess secretion of the adrenal may be concerned in the chronic phase of hypertension following renal artery constriction. The evidence is reviewed by Wilson (1953). It will suffice to say that all the evidence shows to date is that the effects of renal artery constriction, of sodium, and of the adrenal cortex are interrelated and summated. There is no direct evidence of an increased secretion of cortical hormone as the basis of the chronic phase of hypertension due to renal artery constriction.

The effect of adrenal cortical hormones and salt in producing hypertension, and in maintaining that produced by renal artery constriction, has raised the problem as to how far changes in intra- or extra-cellular fluid volume, or in the ratio of cations in the intra-cellular or extracellular fluid, is responsible for the elevated pressure. Eichelberger (1943) estimated Na, K and Cl in serum and muscle from normal dogs and dogs with hypertension produced one or more months previously by clamping the renal arteries. Accepting Cl as confined to extracellular fluid in muscle in hypertension, she concluded that there was an increase in the extracellular fluid volume in skeletal muscle in hypertension, but that there was no significant change in the concentration of intracellular potassium. Laramore and Grollman (1950), in similar observations on rats, concluded that there was a change in the intracellular ratio of cations. Ledingham (1953), in very careful experiments using inulin as an index of extracellular fluid,

has shown that, in heart and skeletal muscle, there is an increase in the extracellular fluid volume in the early stages of renal hypertension, but that this returns gradually to normal over a period of three months, despite the persistence of the hypertension.

Influence of the Carotid Sinus and Aortic Reflexes

In animals with hypertension, produced by renal artery constriction or by perinephritis, clamping the carotid arteries produces an acute rise of arterial pressure and slowing of the pulse. Thus the homeostatic reflexes remain active in renal hypertension. The normal pulse rate suggests that they are not stimulated more than at lower pressures, but as in human hypertension, the available methods are too crude to decide this important point. Heymans (1954) has shown that local application of noradrenaline to the carotid sinus will reduce to normal the blood pressure of dogs with hypertension due to perinephritis. That the reflexes have the power to abolish hypertension suggests that in some way they have become adapted during the sustained rise of blood pressure.

OTHER FORMS OF INTERFERING WITH THE KIDNEYS *in situ*

Since full and excellent reviews of other methods of producing hypertension by renal interference are available elsewhere (Blalock, 1940; Goldblatt, 1947; Braun-Menendez and others, 1946), only a brief summary and comment will be made here.

Varying reports have been published concerning such nephrotoxic agents as lead salts, uranium salts, oxalates and diphtheria toxin. Hartmann, Bolliger and Doub (1926) and O'Hare and others (1926) found that irradiating the kidneys of dogs produced a moderate hypertension, destruction of the renal parenchyma and diffuse fibrosis of the kidneys. These observations were confirmed by Page (1936). More important is the experimental glomerulonephritis produced by anti-kidney serum by Masugi (1934), and which closely resembles histologically the glomerulonephritis found in man. In kidneys from rabbits with this form of glomerulonephritis and hypertension, supplied by Arnott and Keller, Prinzmetal, Kelsall and I (1942) did not find an abnormal renin content.

Removal of one kidney is not usually followed by hypertension in rabbits and rats; but when about half of the other is removed in addition, hypertension generally results. In such animals Dock and Rytand (1937) did not observe a reduction in blood flow per gram of kidney.

Complete occlusion of a renal artery produces variable results, as do multiple renal emboli. Venous obstruction may produce a transitory

hypertension (Bell and Pedersen, 1930; Braun-Menendez, 1933), but this is inconstant; Bell and Pedersen's animals also had the kidney Occlu-
-lusion of
alive by

dialysis this hypertension is transitory.

Partial occlusion of the abdominal aorta above, but not below, the renal arteries produces hypertension, though it may be necessary to constrict the aorta both above and below the kidneys to produce severe and persistent hypertension. This hypertension would seem to be identical in mechanism with that produced by renal artery constriction. Page (1940) has shown that it is not possible to produce hypertension by constricting the aortic arch in dogs, owing to the abundant collateral circulation. Nevertheless, despite species differences, these observations are clearly relevant to the question of coarctation of the aorta in man.

One of the most effective ways of producing hypertension is by inducing an inflammatory reaction around the kidney, by wrapping it in cellophane silk, tape, collodion or latex. Whether this acts by compressing the kidney or by compressing the pedicle is disputed, but is important in view of the doubt concerning the nature of the renal change inducing hypertension. So far as is known, hypertension produced by perinephritis behaves in all ways like that due to renal artery constriction.

Hartroft and Best (1949) have shown that a brief period of choline deficiency in young rats followed by a return to full diet leads to extensive tubular destruction in the kidneys, to hypertension and cardiac hypertrophy that are proportional to the degree of renal destruction; and to vascular lesions, including fibrinoid necrosis of the arterioles, but not elastosis.

HYPERTENSION PRODUCED BY EXCISING THE KIDNEYS

Earlier workers did not observe hypertension from removing one kidney or both. In fact, in the rabbit the blood pressure tends to be reduced after nephrectomy and unchanged after ureteric ligation in the two or three days the animal survives (Pickering, 1945). The first to emphasize the rôle of nephrectomy were Grollman, Harrison and Williams (1943) who produced hypertension

percentage of

it

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producing hypertension in the dog and rabbit, as constricting the renal artery or wrapping the kidney. They, therefore, presented the hypothesis that the contribution of the kidney to hypertension is not so much the addition to the circulating

blood of a pressor substance, as the failure to excrete or destroy a pressor substance. They considered that this hypothesis was supported by their observation that removal of the ischaemic kidney did not abolish the hypertension, the other kidney being untouched. There were two difficulties about these experiments. Firstly, most other workers did not obtain hypertension from excising a single kidney, nor is this procedure effective in man. In the rabbit they unfortunately used the very debatable method of McGregor (1928) to measure blood pressure. Grollman and Halpert (1949) have resolved at least some of this discrepancy by finding that excision of a single kidney in the rat only produces hypertension if the other kidney is abnormal. Secondly, the effect of excising the single ischaemic kidney in the dog, when the other normal kidney is present, is not always what Grollman and his colleagues have found. Nor is it in the rat, and, in this animal, at least two other explanations have been put forward, one of which at least is backed by substantial evidence. For, according to Wilson and Byrom (1941) and to Floyer (1951), excising the clamped kidney abolishes hypertension when the other kidney is free of arteriolar lesions, but not when these lesions have developed.

While, therefore, experiments in which a single kidney is excised before or after constricting its renal artery do not carry conviction, observations on bilateral nephrectomy are more impressive. As Grollman and his colleagues (1949) have shown, if the period of survival after excising both kidneys is prolonged either by feeding the animals with a low protein, electrolyte-free diet or by dialysing their blood by peritoneal lavage or by the artificial kidney, hypertension develops, its severity being approximately proportional to the duration of life.

They have found that if the excretory action of the kidney is prevented by implanting the ureter into the gut, no hypertension develops in the dog. It is concluded, therefore, that the hypertension following nephrectomy is not due to the secretion of a pressor substance by the kidney, nor to the retention of a substance normally excreted by the kidney; by exclusion, the hypertension is attributed to the action of a pressor substance manufactured elsewhere and normally destroyed by the kidney. These results have been amplified in parabiotic rat pairs, in which the skin and abdominal muscles are sutured together in the flanks. Removal of both kidneys from one member usually produces hypertension in that animal but not in its fellow. A greater incidence of hypertension may occur in the nephrectomized central member of parabiotic triplets. Braun-Menendez and Covian (1948) found that the extent to which hypertension develops is related to the extent to which plasma volume and intracellular volume are raised in the nephrectomized member, and the hypothesis has been presented that the hypertension is due to retention of sodium chloride

and water. Ledingham's (1951) experiments showing the dependence of this hypertension on the presence of the adrenals would seem to support this, but Ledingham himself, in a very few experiments, was unable to raise arterial pressure in the rat by injections of saline, plasma, blood and packed cells.

Thus, it has been shown that removing the kidneys will, after a latent period of a few days, produce hypertension. The mechanism of this hypertension has not yet been securely established. It may be related to adrenal function, but it is conceivable that the effects of kidney and adrenal removal are merely summated. It is also to be remembered in this connection that the effect of nephrectomy in augmenting the response to renin has never been satisfactorily explained. Finally, it is to be emphasized that, while it is possible that the mechanism of hypertension following nephrectomy is the same as the chronic

Renotrophin

To account, by a single hypothesis, for the different methods of producing hypertension, Braun-Menendez (1952) has put forward the idea that both kidney size and arterial pressure are determined, *inter alia*, by the concentration in the blood of a single substance at present purely hypothetical, renotrophin, which may be an intermediate product of protein metabolism. "There is normally an equilibrium between ~~renin and renotrophin~~ ^{renin and renotrophin} transform causes by equilibrium ~~renin and renotrophin~~ ^{renin and renotrophin} remaining renal tissue is unable to respond to the stimulus of the normal or increased amounts of renotrophin present in blood, hypertension develops."

B. HYPERTENSION PRODUCED BY NORMAL BODY CONSTITUENTS

Infusion of Renin

It has already been mentioned that, provided strict asepsis is maintained, intravenous infusion of rabbit renin into the rabbit produces sustained hypertension with cardiac hypertrophy. The intensity of the hypertension seems to be proportional to the logarithm of the dose up to a certain point beyond which there is no increase in blood pressure; up to this point, provided the dose is kept constant, the arterial pressure tends neither to fall nor rise if the infusion is continued at a constant rate. Failure of previous workers may be due to sepsis, to using renin made from another species, or to dosage (Blacket and others, 1950; Pugh and others, 1952).

blood of a pressor substance, as the failure to excrete or destroy a pressor substance. They considered that this hypothesis was supported by their observation that removal of the ischaemic kidney did not abolish the hypertension, the other kidney being untouched. There were two difficulties about these experiments. Firstly, most other workers did not obtain hypertension from excising a single kidney, nor is this procedure effective in man. In the rabbit they unfortunately used the very debatable method of McGregor (1928) to measure blood pressure. Grollman and Halpert (1949) have resolved at least some of this discrepancy by finding that excision of a single kidney in the rat only produces hypertension if the other kidney is abnormal. Secondly, the effect of excising the single ischaemic kidney in the dog, when the other normal kidney is present, is not always what Grollman and his colleagues have found. Nor is it in the rat, and, in this animal, at least two other explanations have been put forward, one of which at least is backed by substantial evidence. For, according to Wilson and Byrom (1941) and to Floyer (1951), excising the clamped kidney abolishes hypertension when the other kidney is free of arteriolar lesions, but not when these lesions have developed.

While, therefore, experiments in which a single kidney is excised before or after constricting its renal artery do not carry conviction, observations on bilateral nephrectomy are more impressive. As Grollman and his colleagues (1949) have shown, if the period of survival after excising both kidneys is prolonged either by feeding the animals with a low protein, electrolyte-free diet or by dialysing their blood by peritoneal lavage or by the artificial kidney, hypertension develops, its severity being approximately proportional to the duration of life.

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Renotrophin

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hypertension, renotrophin, which may be an intermediate product of protein metabolism. "There is normally an equilibrium between

the stimulus, atrophy of the kidneys. When this equilibrium is broken and the remaining renal tissue is unable to respond to the stimulus of the normal or increased amounts of renotrophin present in blood, hypertension develops."

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(1949) found that removal of 75 mg. DCA pellets, at times up to fifty-one days after implantation, restored the arterial pressure to normal in six days. Prado (1950) found that when pellets had been implanted for 140 days, their removal was not followed by restoration of blood pressure in thirty-four days, though, when left a shorter period, residual hypertension was irregular. The explanation of this residual hypertension and particularly its relation to renal lesions is uncertain.

Anterior pituitary hormones, particularly the growth hormone, can produce hypertension in the rat. Dontigny and others (1948) have shown that the production of hypertension and nephrosclerosis by a certain dose of the hormone depends on an adequate protein content of the diet.

DCA and salt produce cardiac hypertrophy and nephrosclerosis and presumably hypertension also in the chick. They are much less effective in the dog and rabbit (for review see Masson and others, 1953).

C. HYPERTENSION PRODUCED BY SECTION OF THE CAROTID SINUS AND DEPRESSOR NERVES

Hering's (1927) demonstration of the importance of the reflex

... of hypertension in man (see Chapter 7), and his pupils to study the effects of section of the carotid sinus and depressor nerves in the experimental animal. Koch, Mies and Nordmann (1927) showed that, in rabbits, section of the carotid sinus and depressor nerves on both sides at a single operation is usually fatal because of fibrillation of the heart and pulmonary oedema. If, however, an interval of ten to fourteen days separates the operations on the two sides the animals usually

by arterial cannulae

1929) The hyperten-

accompanied by tachycardia and it was always reduced by a variety of stimuli such as pricking the skin, blowing on the nasal mucosa, movement, pressure on the larynx, etc., which give a rise of pressure in the normal animal. Since, in many experiments, the animals were stretched on a board without narcosis, and with tracheal and arterial cannulae in place, it may be thought that the circumstances of the experiment had already produced a maximal rise of arterial pressure before additional stimuli were employed. Others have pointed out that the arterial pressure, in animals so operated, is much more susceptible than usual to splanchnic section, injection of vaso-active substances and haemorrhage (Hering, 1927; Heymans, Bouckaert and Regniers, 1933).

Infusion of Adrenaline and Noradrenaline

Using exactly the same technique as had been used successfully for renin, Blacket, Pickering and Wilson (1950) found that infusions of adrenaline or of noradrenaline, or of mixtures of the two would not maintain hypertension for more than a few days even though the dose was increased. The animals tended to become ill, and one died; the large gut was distended with gas at post-mortem, and the faecal pellets were small and wet. The failure of hypertension to be sustained was apparently not due to reduction in plasma volume, as seems to have occurred in earlier experiments on anaesthetized animals with larger doses, for hæmo-concentration was not found. After terminating the infusion, the ears flushed and there was a prompt fall of arterial pressure to well below the preliminary level. It was suggested, therefore, that a depressor substance had been produced in the body during the infusion of adrenaline and noradrenaline.

Although sustained hypertension was not produced, the ratio of cardiac weight to carcase weight was increased in rabbits receiving adrenaline or noradrenaline infusions, and the increase was greater than could be accounted for by loss of body weight. No vascular lesions were found (Pugh, Pickering and Blacket, 1952).

Salt and the Adrenal Cortical Hormones

It has been known for many years that high blood pressure can be reduced by starving the patient of salt. After the preparation of potent adrenal cortical extracts and their therapeutic use in Addison's disease, it was noticed that overdosage produced hypertension. Both sodium chloride and the adrenal cortical hormones have therefore been extensively used to produce hypertension in laboratory animals (for reviews see Selye, 1951; Braun-Menendez, 1951).

By far the most suitable animal seems to be the rat. If desoxycorticosterone acetate (DCA) is given in doses of 2.5 mg. per day or as implants of 40 mg. and the animals receive 1.0 per cent. NaCl instead of water to drink, hypertension is produced regularly, and is regularly accompanied by increased heart weight, increased kidney weight and increased blood volume. If the diet is salt free, DCA, even in larger doses, produces no hypertension. Two per cent. NaCl used as drinking fluid for six weeks also produces hypertension and renal hypertrophy (Sapirstein and others, 1950). Selye and his colleagues have paid particular attention to the histological changes produced, finding the changes of malignant nephrosclerosis in the kidney, nodules resembling Aschoff nodes in the heart, and arterial lesions resembling polyarteritis nodosa elsewhere. These findings are the basis of Selye's well-known hypothesis of the diseases of adaptation. Friedman and Friedman

cardia, but being normal or nearly so when the animal is quiet or asleep. In these features, this condition differs from experimental renal hypertension and most cases of so-called essential hypertension in man. There are, however, certain cases of so-called essential hypertension in which the arterial pressure is also extremely unstable, and in which hypertension is accompanied by tachycardia and the possibility exists that these, likewise, are due to an abnormality in the nervous mechanisms regulating arterial pressure.

D. HYPERTENSION PRODUCED BY INTERFERENCE WITH THE BRAIN

Intracisternal Injection of Kaolin

Dixon and Heller (1932) showed that in dogs injection into the cisterna magna of 20 mg. Kaolin per kg. led to a rise in c.s.f. pressure, and to a rise of arterial pressure persisting many months. In four such animals, cardiac hypertrophy was found in only one; nor was any lesion found in large or small arteries. Thirteen additional animals were studied by Hamperl and Heller (1934), who measured the arterial pressure by a thigh cuff. No cardiac hypertrophy was found, nor any conspicuous abnormality of the vessels. They concluded that, in this respect, the hypertension resembled that due to denervation of the

... (1934) stated that this type of hypertension was abolished by denervating the kidney, and subsequently restored by removing the denervated kidney. This bizarre experiment has not, apparently, been repeated. The hypertension is not abolished by adrenalectomy, provided sufficient cortical extract is given to keep the animals well (Jeffers, Landauer and Lukens, 1937).

Hypertension Produced by Cerebral Ischaemia

Nowak and Walker (1939) published the blood pressure chart of one dog in which hypertension had been produced by successive ligation of the carotids, the vertebrals and the anterior spinal arteries. They indicated that this was not an easy procedure, owing to the ease with which collaterals developed. They gave no details of how the pressure was measured. Rosenfeld (1952) claims to have done the same in rabbits in which, unfortunately, he used chiefly McGregor's (1929) method for measuring arterial pressure. However, by femoral artery puncture under anaesthesia he found average ...
vert.
serv

... their nerves.

The production of hypertension by section of the four buffer nerves has been confirmed by Kremer, Wright and Scarff (1933) in the rabbit, using the carotid loop to measure arterial pressure and in the dog by Heymans and Bouckaert and their numerous pupils. Others have found hypertension less commonly after nerve section (see Goldblatt, 1947).

This type of hypertension is dependent on the integrity of the sympathetic nerves. It does not occur in the totally sympathectomized animal. In the dog, it is accompanied by an increase in cardiac output and blood flow to the limb (Bing, 1944).

The anatomical changes found in this type of hypertension differ in two important respects from those found in experimental, renal and in most types of human hypertension.

(1) Arteriolar necroses have never been described (Kremer, Wright and Scarff, 1933; Nordmann, 1929), even in animals in which the arterial pressure seems to be higher than after constriction of the renal arteries. Grimson (1941) has cited this as evidence against the hypothesis (p. 92) which attributes these lesions to a greatly raised arterial pressure.

(2) The degree of cardiac hypertrophy seems to be less. Thus Nordmann (1929) found that in six rabbits with arterial pressures of between 120 and 141 mm. Hg, lasting for five to seventeen months, the heart body weight ratio was — 11 per cent. to + 26 per cent.

the normal, while in seven rabbits with arterial pressures between 145 and 171 mm. Hg for three and a half to ten and a half months, the heart weight was +11.4 to +30 per cent. of the normal. In Pickering and

Prinzmetal's (1938b) series of 32 normal rabbits, $\frac{\text{heart weight} \times 100}{\text{body weight}}$ had

a mean value of 0.254 and limits of 0.20 and 0.33. In the more severely affected of Nordmann's groups, the heart weights were all above this mean but only two above the normal limits. In Pickering and Prinzmetal's rabbits with renal hypertension (arterial pressure 100 to 150 mm. Hg in the central artery of the ear) the heart weights of four were within the upper normal range, while 12 were above, and of those, three were above twice the normal size.

These two peculiarities are explained by an observation of Heymans and Bouckaert (1934), confirmed by Samaan (1934), which has not received the attention it deserves. These authors showed that after section of the buffer nerves, the arterial pressure is elevated in the unanæsthetized dog only when the animal is awake and excited; when the animal is quiet or asleep, the arterial pressure is normal. The arterial pressure is also raised in the anaesthetized animal.

To summarize, it would seem that after section of the carotid sinus and depressor nerves, the arterial pressure is extremely unstable, reaching very high levels under anaesthesia or during excitement in the conscious animal, and then accompanied by conspicuous tachy-

SUMMARY

In previous chapters we saw how the arterial pressure was regulated, and protected against change, by mechanisms of great power and delicacy. In this chapter, the extent to which it is possible to produce a sustained elevation of arterial pressure has been reviewed. Interference with the major homeostatic reflexes by section of the carotid sinus and depressor nerves produces an extremely labile arterial pressure, that probably gives an exaggerated idea of the persistence of high blood pressure, because the circumstances of measurement are such as usually produce the highest pressures; cardiac hypertrophy is relatively slight and arteriolar necroses have not been described. Renin infusion produces a persistent hypertension with cardiac hypertrophy and possibly arteriolar necroses. For reasons that are still unknown, infusions of adrenaline and noradrenaline fail to produce persistent hypertension, though they seem to produce cardiac hypertrophy. Overdosage with salt and adrenal cortical hormones such as DCA, produces hypertension with malignant nephrosclerosis in the rat and chick, but less satisfactorily in dog or rabbit.

It was pointed out earlier that the major homeostatic mechanisms seem to regulate the arterial pressure in the interests of brain, heart and kidneys. There is suggestive but not conclusive evidence of interference with the blood supply though the whole problem needs study. Interference with blood supply to the kidneys produces undoubted and persistent hypertension with cardiac hypertrophy and arteriolar necroses.

In its chief features, hypertension due to renal artery constriction has a close resemblance to the commoner forms of hypertension in man, and there is a reasonable hope that discoveries in the one field may illuminate the other. It is, therefore, a little disappointing that the mechanism of hypertension

though by no means all, favours renin as the humoral agent. Later another, and probably extrarenal, factor comes into action and may be, itself, sufficient to sustain the raised pressure. The nature of this later change is at present quite unknown.

Standing alone as a curiosity of experimental medicine is the hypertension produced by excision of both kidneys, easily demonstrated only when animals are kept alive beyond their allotted span by parabiosis, dialysis and other measures. While this condition has no direct relevance to human disease, the elucidation of the mechanism by which the arterial pressure is raised may throw unexpected light on problems now hidden in darkness.

Taylor and Page (1951) have made experiments on 165 dogs. Ligature of arteries supplying the head, extensive enough to kill 41 per cent. of the animals, induced arterial hypertension in only 24 per cent. of those that lived, often associated with signs of transient dementia, the hypertension lasting only seven to twenty-five days. A longer rise of pressure, lasting two to ten months was induced in 64 per cent. of dogs by combining cerebral ischæmia with stimulation of a tantalum wire, inserted in the floor of the fourth ventricle, heated by shortwave diathermy.

E. HYPERTENSION PRODUCED BY STRONG SENSORY STIMULI

As will be seen in Chapters 8, 9 and 10, there is a good deal of evidence that what is called essential hypertension in man is the result of the interplay of genetic and environmental factors. It is of very great interest therefore to learn that in the rat hypertension can be produced by repeated exposure to strong sensory stimuli, but only in rats of suitable genetic constitution. By repeated exposure of rats to the sound of an air blast, Medoff and Bongiovanni (1945) produced hypertension which persisted under ether anæsthesia. Farris, Yeakel and Medoff (1945) exposed 12 gray Norway rats to this noise for 167 days, and noted some relationship between the degree of "emotionality," as assessed by an objective test before blasting, and the incidence of hypertension. Smirk (1949) confirmed these observations and noted that hypertension persisted when the stimulus was withdrawn. Rothlin (1954) failed to produce hypertension in rats of the Glaxo laboratory strain by exposing them to bells and hooters and flashes of light for more than twelve months. When, however, the experiments were repeated with rats bred by crossing the laboratory rat with the wild rat, then auditory stimuli alone proved sufficient to induce hypertension. Daily exposure to five minutes of cacophony produced an increased blood pressure in two months, the rise being maximal at four to five months and continuing as long as the stimulus. No changes were found in the vessels, but the ratio of heart weight to body weight was raised. If after four months the stimulus was discontinued, the arterial pressure remained unchanged for thirty days; was clearly reduced after two months and reached normal after four months. A second exposure to the same stimuli produced in one month a rise equivalent to that which had previously taken three months to be produced. The rise could be prevented by hydrogenated ergot alkaloids. Two per cent. salt solution as drinking fluid produced hypertension in unexposed rats, but paradoxically enough, hypertension so produced was reduced when the rats were exposed to the horrid noise.

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It was pointed out earlier that the major homeostatic mechanisms seem to regulate the arterial pressure in the interests of brain, heart and kidneys. There is suggestive, but only slight, evidence that interference with the blood supply to the brain will produce hypertension, though the whole problem needs a much more detailed and critical study. Interference with blood supply to the kidneys produces undoubted and persistent hypertension with cardiac hypertrophy and arteriolar necroses.

In its chief features, hypertension due to renal artery constriction has a close resemblance to the commoner forms of hypertension in man, and there is a reasonable hope that discoveries in the one field may illuminate the other. It is, therefore, a little disappointing that

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CHAPTER II

THE CLASSIFICATION OF HYPERTENSION

THE object of classification is to group like with like and to separate unlike, so that knowledge gained on one group of individuals may with confidence be applied to another similar group. With the advance of knowledge, particularly of the mechanism and ætiology of disease, conditions previously thought to be alike are shown not to be so, and *vice versa*. Any classification is thus always to be regarded as temporary, and likely to be replaced by a better.

HISTORY

The history¹ of the classification of hypertension reflects our increasing understanding of its ætiology and pathogenesis. It is, of course, to be remembered that estimates of arterial pressure only began to be made in the middle of last century and were then often quite inaccurate; they became an established clinical procedure only in this, the twentieth century. High blood pressure was thus at first known very largely from the presence after death of an otherwise unexplained cardiac hypertrophy. The three chief abnormalities found after death affected the kidneys, the heart and the vessels, and the inter-relationship of these changes has always been the focal point of any attempts to understand pathology and to classify.

The story begins with Bright (1827), who described meticulously a series of cases in which albuminous urine was associated with dropsy. He noted three types of kidney; one he thought was degenerative (probably amyloid) and the other two might be different stages of the same disease. In his "Tabular View of the Morbid Appearances in 100 Cases Connected with Albuminous Urine" Bright (1836b) wrote: "The obvious structural changes in the heart have consisted chiefly of hypertrophy with or without valvular disease; and what is most striking, out of fifty-two cases of hypertrophy, no valvular disease whatsoever could be detected in thirty-four: but in eleven of these thirty-four, more or less disease existed in the coats of the aorta; still, however, leaving twenty-two² without any probable organic cause for the marked hypertrophy generally affecting the left ventricle. This naturally leads us to look for some less local cause, for the unusual

¹ Fuller accounts are given by Volhard (1931) and by Wagener and Keith (1939).

² These figures are those given by Bright: one seems to have gone astray.—G. W. F.

efforts to which the heart has been impelled ; and the two most ready solutions appear to be, either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately ; or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant subdivisions of the vascular system."

In Britain, clinicians were occupied, for the next thirty or forty years, in attempting to classify Bright's disease and in enquiry whether the cause was single or multiple. Amongst them, Samuel Wilks (1853), also of Guy's Hospital, wrote : " Among these were two very remarkable extreme conditions—the one a kidney large and white, often double the natural size, and associated with a very considerable dropsy of the whole body, the other a kidney hard and contracted, often only half the usual size, chronic in its character, and often destitute of symptoms." These two varieties, the large white kidney and the small white kidney, were later distinguished (Bartels, 1877) as chronic parenchymatous and chronic interstitial nephritis ; they are now considered as the end stages of the types I and II of nephritis of Ellis

So far as hypertension is concerned the next landmark is the paper of Gull and Sutton (1872) on " Arterio-capillary fibrosis." Gull and Sutton concluded : " That the arterioles throughout the body in that condition usually called chronic Bright's disease with contracted kidney, are more or less altered. That this alteration is due to a ' hyalin-fibroid ' formation in the walls of the minute arteries and a

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on their finding three forms of the disease :
 " (1) Kidneys often much contracted, heart much hypertrophied, minute arteries and capillaries proportionately thickened by ' hyalin-fibroid ' formation (2) Kidneys little contracted, but heart much hypertrophied, minute arteries and capillaries much thickened by hyalin-fibroid substance. (3) Kidneys healthy, whilst heart much hypertrophied and minute arteries and capillaries much thickened by hyalin-fibroid substance "

Meanwhile clinicians were learning to estimate, however inaccurately, the arterial pressure by the tension of the pulse and the characters of the pulse-tracing. Mahomed (1879), the last of these outstanding contributors of the Guy's Hospital School, was the first to make full use of the blood pressure estimated during life. He wrote two particularly important papers on chronic Bright's disease, in which

CHAPTER 6

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natural, but by no means the invariable, termination of the disease." He showed that termination by renal failure was only one outcome of chronic Bright's Disease without albuminuria and that death occurred more commonly from heart failure or cerebral hæmorrhage. He also showed that the final form of Bright's disease could be produced in other ways. "The disease may commence as an acute affection and afterwards become chronic. . . . What has been cause in one case may be the result in another; thus general disorder may cause high arterial pressure, and this, in its turn, kidney changes; while, on the other hand, kidney changes may be primary and acute, and they may in their turn produce impurity of blood, and this general high pressure. But whether we read the tale backwards or forwards it is the same tale in the end." Thus Mahomed anticipated Volhard and Fahr by some thirty-three years. That this work was so little known may be partly ascribed to his having died of typhoid fever at the age of thirty-five (Batty Shaw, 1952).

Meanwhile in Germany, Traube had suggested that arteriosclerosis and hypertrophy of the heart were the co-ordinated effects of a primary rise in arterial pressure. Others, however, took the view that the rise in pressure was a consequence of arteriosclerosis (see Romberg, 1924). Ewald (1877), examining chiefly the small vessels of the pia mater, confirmed Johnson's (1868) finding of a hypertrophy of the media which he found correlated with hypertrophy of the heart and regarded as a consequence of hypertension. Jores (1904) did not deny that the arterial media could hypertrophy in nephritis but he regarded the changes in the intima as more characteristic and important. He found fatty hyaline thickening of the intima of the small arteries narrowing, and sometimes obliterating, the lumen not only in the kidney, but also in the spleen, the brain and the pancreas, less frequently in stomach, intestines and liver, but not in the heart or skeletal muscle. He thought these changes were not simply an end-result of nephritis and that they might materially influence the course of the disease.

The recognition that there is a condition which may pursue a course quite different from Bright's disease of the kidneys we owe largely to von Basch, Huchard and Allbutt. Von Basch (1893), who made very many estimations of arterial pressure, was well acquainted with what we now call essential hypertension, which he called latent arteriosclerosis.

In France, Huchard (1889) recognized clearly that hypertension might occur independently of nephritis. He wrote: "L'hypertension permanente . . . a été regardée à tort . . . à la néphrite interstitielle à laquelle elle précède pendant un temps . . .".

he anticipated so accurately the modern view that his words will be quoted extensively. In the first (1879), he analysed the clinical aspects of 100 cases of granular kidneys. Of these, 74 had red granular kidneys and presented symptoms of disease other than Bright's disease; 17 of them "died with all the ordinary symptoms of heart disease, and 15 died of apoplexy, making 32 deaths directly due to cardio-vascular changes"; 18 died of lung disease and 24 of other medical and surgical diseases. "In a very large proportion of these 74 cases albuminuria was absent." Only 26 presented with the ordinary symptoms of Bright's disease and these showed a mixed granular kidney with epithelial excess at necropsy. Attempting to find a unitary explanation for all these cases, he wrote as follows: "This view" (that of Bright and subsequent writers) "makes the kidney changes primary, the cardio-vascular secondary. I have tried, however, to prove that this sequence of events should be reversed; namely, that a poisoned condition of the blood is the primary condition, that this produces an impeded circulation through the capillaries, and subsequently the cardio-vascular changes." "The arguments upon which this hypothesis has been based are as follows:—First, that high arterial pressure is found to exist before any sign of failure of the kidneys to perform their function occurs. Second, that certain poisons are known to produce kidney disease, and that these poisons produce high pressure in the arteries, while no symptoms of kidney failure are discoverable. . . . Third, the condition of high pressure is found to occur in some young people, in all other respects perfectly healthy. . . . such patients very often have a family history of gout or Bright's disease, and if they live long enough, will almost inevitably develop it themselves. Fourth, far from the kidney disease being the primary condition, I find that patients with primary kidney disease, such as is seen in surgical kidneys or scrofulous kidneys, even of the most advanced nature, do not have high pressure in their arteries, while patients with acute Bright's disease, if the poison be acute and temporary, may lose all signs of high arterial pressure during their recovery, even at a time when the kidneys are manifestly crippled, the urine being albuminous and the solids deficient in amount." In his 1881 paper on chronic Bright's disease without albuminuria, Mahomed wrote: "From these considerations it follows that we have to deal with three stages of chronic Bright's disease: first, the *functional stage*, which is limited to the condition of high arterial pressure without organic changes in either the vascular system or the kidneys; second, the *chronic Bright's disease without nephritis*, the stage of organic changes in the vascular system and in the kidney (for which, if thought desirable, the term 'arterio-capillary fibrosis' might be employed); third, chronic Bright's disease with nephritis, the

- | | |
|---|---|
| 1. Acute stage. | } All three stages can run :
(a) without nephrotic onset. ¹
(b) with nephrotic onset. ¹ |
| 2. Chronic stage without renal insufficiency. | |
| 3. End stage with renal insufficiency. | |

C. Arteriosclerotic diseases : sclerosis.

- (1) Simple benign hypertension = pure sclerosis of the renal vessels.
- (2) The combination form : malignant genuine contracted kidney = sclerosis + nephritis.

The great virtues of this classification were the subdivision of renal diseases into three major groups and the recognition of what is now

recognized owing largely to Longcope (1937) ; and our conception of malignant hypertension has changed partly owing to the work of Volhard and Fahr themselves, but chiefly because of work described in Chapters 5, 11 and 13, which suggests strongly that the benign and malignant phases of hypertension are consequences of the intensity of the hypertension, irrespective of the way this is produced. Here we are concerned primarily with high blood pressure, and with renal abnormalities only so far as they are, on the one hand, the cause and, on the other, the consequence of hypertension. The following classification of hypertension is proposed and will be used in this book.

PROPOSED CLASSIFICATION OF HYPERTENSION

A. SYSTOLIC HYPERTENSION, IN WHICH THE SYSTOLIC PRESSURE ONLY IS RAISED

- I Due to increased stroke output of the heart (Conditions listed on p 46)
- II Due to increased rigidity of the aorta

B. HYPERTENSION IN WHICH BOTH SYSTOLIC AND DIASTOLIC PRESSURES ARE RAISED

(a) Classification by kind :

I Secondary hypertension

- (1) :

¹ See Chapter 15 for meaning of "nephrotic"

diverses maladies (cardiopathies et néphrites artérielles etc.), lesquelles sont elles-mêmes sous la dépendance de la sclérose vasculaire." Huchard named the condition presclerosis. At the same time, Allbutt had observed the occurrence of raised arterial pressure in the absence of albuminuria. In 1895 he described five cases under the term "senile plethora." In 1915 he wrote: "Thus gradually I became convinced that cases, such as we are considering, must be divided, first, into Bright's Disease . . . secondly, into the class to which soon afterwards I gave the name *Hyperpiesis*, a malady in which at or towards middle life blood pressures rise excessively, a malady having a course of its own and deserving the name of a disease; and thirdly, into at least one other class of arterial degeneration, one not typically associated with rise of blood pressure, a class in which indeed the blood pressure does not exceed, or scarcely exceeds, the rise common to almost all persons in later life; a series of which the course, symptoms, and issues are altogether different." To this third class Allbutt gave the name "decreascent" arteriosclerosis. Allbutt's classification has been expanded and modified; yet in its bare outline it remains acceptable. His term *hyperpiesis*, however, never became widely used. Frank's term "*essentielle Hypertonie*" (1911) became widely used and has been a little oddly translated into English as *essential hypertension*.

VOLHARD AND FAHR'S CLASSIFICATION

The modern classification dates from Volhard and Fahr's *classical* combined clinical and pathological study. Their (1914) classification was as follows:

- A. Degenerative diseases: Nephrosis, "genuine" and of known aetiology, with and without amyloid degeneration of the vessels.
 - (1) Acute course.
 - (2) Chronic course.
 - (3) Final stage: nephrotic contracted kidney without rise of blood pressure.
- B. Inflammatory diseases: nephritides.
 - (1) Focal nephritides without rise of blood pressure.
 - (a) Focal glomerulonephritis.
 1. Acute stage.
 2. Chronic stage.
 - (b) (Septic) interstitial focal nephritis.
 - (c) Embolic focal nephritis.
 - (2) Diffuse glomerulonephritis with obligatory rise of blood pressure. Course in three stages:

would be more prone to cardiovascular accidents, such as myocardial infarction and dissecting aneurysm, than those without elevated systolic pressures, but I know of no evidence bearing on the question. This form of hypertension will not be further considered in this book; the degenerative vascular changes of the aorta and large arteries will be described in Chapter 11.

SYSTOLIC AND DIASTOLIC HYPERTENSION

Here we may infer that mean pressure is also raised. For a given diastolic pressure the systolic pressure is the more greatly raised if the aorta is small, as in coarctation, or if it is rigid as it tends to be in elderly subjects.

This form of hypertension is the subject of the remainder of this book.

The Classification by Kind and by Degree

The new classification proposed is a two-way classification by kind and by degree. Previous classifications make no attempt to differentiate between qualitative and quantitative differences.

In the first classification, that of kind, an attempt has been made to separate the different disease entities in which hypertension may be a prominent symptom, in each of these, the actual mechanism by which the pressure becomes raised may or may not be peculiar to that disease, and in each, cure of the underlying disease should cure hypertension. The second classification, that of degree, is an innovation. Since Volhard and Fahr's classification of 1914, it has been known that essential hypertension may remain stable for many years, or may follow a rapidly progressive course, with albuminuric retinitis, rapid renal failure and the presence after death of acute arteriolar necroses. These so-called benign and malignant courses are known to occur in a small number of cases.

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essential hypertension, pyelonephritis or Cushing's syndrome. By using this two-way classification, it is possible first to designate the kind of hypertension, e.g. secondary to pyelonephritis, or essential hypertension, and second to decide whether it is in the benign or malignant phase. The use of the two-way classification thus makes diagnosis, as it should be, the appropriate introduction to exact the

with
by

- (b) Type II nephritis¹; in the terminal stage.
 - (c) Chronic pyelonephritis, unilateral or bilateral.
 - (d) Polycystic kidney.
 - (e) Renal stone and other lesions obstructing the urinary tract.
 - (f) Vascular lesions of the kidney.
 - (g) Amyloid contracted kidney.
 - (h) Radiation nephritis.
 - (2) Coarctation of the aorta.
 - (3) Pheochromocytoma.
 - (4) Cushing's syndrome.
 - (5) Polyarteritis nodosa.
 - (6) Pre-eclamptic toxæmia of pregnancy.
 - (7) Post-toxæmic hypertension.
- II. Essential hypertension.

(β) Classification by degree :

I. Benign phase.

II. Malignant phase.

The division between normal arterial pressure and each of these degrees of hypertension is not clear cut ; in fact, they merge into each other and into normality, because our attempt to classify overlooks the facts that variation is continuous and that the difference between hypertension and normality is quantitative and not qualitative (see Chapters 8 and 9).

SYSTOLIC HYPERTENSION

Raised systolic without raised diastolic pressure implies a raised pulse pressure, without usually more than an insignificant rise in mean pressure. This occurs in many conditions listed on page 46, which increase the stroke output of the heart, and which have physical signs by which they may be recognized. As age advances, both systolic and diastolic pressures tend to rise but in the older age groups systolic becomes much more elevated than diastolic (Fig. 8.1). It is thus not uncommon in elderly subjects to find moderately high systolic pressures (e.g. 170 mm. Hg) with relatively low diastolic pressures (e.g. 70 or 80 mm. Hg), and to find no other abnormal signs in the cardiovascular system. This systolic hypertension, as it is called, is probably a manifestation of degenerative changes in the aorta and its largest branches, rendering them more rigid (page 43). I suspect that the condition is more common in those with diabetes than those without. It is sometimes associated with calcification of the aortic arch demonstrated on the roentgenogram. One might suspect that such patients

¹ See Chapter 16 for definition.

CHAPTER 7

THE CIRCULATION IN ESSENTIAL HYPERTENSION

In this chapter we approach the problem of essential hypertension from a physiological point of view. The question we ask is what is the basic fault, or faults, in the circulation, of which the raised arterial pressure is the outward sign?

CARDIAC OUTPUT AND BLOOD VISCOSITY : THE PERIPHERAL RESISTANCE

In Chapter 4 the relationship between cardiac output, arterial pressure and the frictional resistance to the flow of blood through the vessels was discussed. The peripheral resistance may be calculated from the following equation.

$$R = P_m / V \text{ sec.} \times 1,332 \text{ dynes cm.}^{-3} \text{ sec.}$$

where R = peripheral resistance.

P_m = mean blood pressure in mm. Hg.

$V \text{ sec.}$ = cardiac output in ml. per sec.

Since the mean pressure is expressed in millimetres of mercury, the factor of 1,332 is introduced to express the peripheral resistance in absolute units (1 mm. Hg equals 1,332 dynes/cm.²).

The cardiac output has been measured in essential hypertension by nearly every method that the ingenuity of man has devised, and, with the more reliable methods, has been found within the normal range. Using the Fick method and cardiac catheterization, Goldring and Chasis (1944) found the total peripheral resistance in nine normal subjects lay between 1,100 and 1,755 dynes cm.⁻⁵ sec., and in six subjects with hypertension between 1,615 and 3,550 dynes cm.⁻⁵ sec.

Since the blood viscosity in essential hypertension is also within the normal limits (Pickering, 1936b), the cause of the increased frictional resistance to the passage of blood through the vessels must be due to abnormalities in the vessels themselves.

... measured the pressure in the brachial and digital arteries in 25 subjects with normal pressure and 51 patients with hypertension. The brachial-digital gradient was the same in essential hypertension as in normal subjects, but increased in a patient with pheochromocytoma. They therefore

Essential Hypertension

It will be noted that in the first classification, that of kind, there are two rather dissimilar groups, that in which hypertension is merely a manifestation of a well-defined disease entity, and that of essential hypertension in which hypertension and its consequences constitute the disease. By current practice which takes not a very high figure, such as 150/100, as the lower limit of hypertension, essential hypertension becomes by far the commonest form of hypertension. It is very commonly supposed that essential hypertension is a clinical entity. Our recent work has made us doubt this. Essential hypertension represents no more than that section of the population having arterial pressures above a certain level, selected on arbitrary grounds, and having no disease to account for these arterial pressures. There is a good case for supposing that the causes of essential hypertension are to be sought in the hereditary and environmental factors which determine the arterial pressure in the population at large. It is, therefore, proposed to consider the behaviour of the arterial pressure with age in the population at large, the rôle of inheritance and the rôle of environment in determining arterial pressure before dealing with the concept of essential hypertension. For it would seem that it is of these ingredients that the problem of the ætiology of essential hypertension is composed. Attempts to define the nature of the basic fault in essential hypertension will be considered in the next chapter.

injecting novocaine around the cervicodorsal sympathetic ganglion. These observations are now largely of historical interest because, as Grant and Pearson (1938) showed later, the flows, measured without previous arrest of the circulation to the hand, are mixed hand and forearm and because two tissues, muscle and skin, were involved.

The Skin. The blood flow through the skin can be conveniently determined in the digits and hand either with a calorimeter or plethysmograph, which, in the hand (Cooper and others, 1949), give very similar results. In the finger, as Greenfield and Shepherd (1950) showed, the plethysmographic method may give results that are too low. Skin blood flow is regulated through the vasomotor nerves in the interests of body temperature regulation (Lewis and Pickering, 1931; Pickering, 1932). The fact that, under given environmental circumstances, the blood flow through the skin is of the same order in normal subjects and subjects with hypertension may mean no more than that the mechanisms for the dissipation of heat from the body are the same in the two groups. The circulation through the skin is peculiarly suited for testing the hypothesis that the increased peripheral resistance is due to overaction of the sympathetic nerves. It was shown (Pickering, 1936b) that heating the body released sympathetic tone completely from the vessels of the hand, since anaesthetization of the ulnar nerve at the elbow did not further increase blood flow; under these circumstances, the blood flow through the hand was the same in subjects with persistent hypertension as in normal subjects. It seemed clear, therefore that, in the hand, the vessels were narrowed by a non-nervous agent, and that this narrowing was of a degree such that, if generally distributed over the body, it would account for the arterial pressures observed. Mendlowitz and Touroff (1952) have reported similar results for the great toe. Stead and Kunkel (1949) obtained similar blood flows through the hand at 43° C. in normal subjects and in subjects with essential hypertension.

It should be remembered that hand, foot and digits are rather peculiar tissues from the vascular point of view, since they have large numbers of arteriovenous anastomoses.

Muscle. When a plethysmograph is placed as high as possible on the forearm, Grant and Pearson's (1938) observations indicate that 85 per cent. of the tissue enclosed is muscle, the remainder being bone and skin. Abramson and Fierst (1942) found that, with the plethysmograph maintained at 32° C, the blood flow was 100 ml per 100 ml tissue per minute in normal or hypertensive subjects during their systolic blood pressure.

From these observations it would seem, therefore, that the higher the systolic pressure, the greater was the forearm blood flow. Similar results were obtained in the calf. From these observations it would seem, therefore,

concluded that the increased resistance lay entirely distal to the digital arteries in essential hypertension and partly proximal to it in phaeochromocytoma. The capillary pressure measured in the skin by the capsule method has been found normal (Ellis and Weiss, 1929); in two cases of malignant hypertension, in which I measured the capillary pressure in the nail fold by Landis' (1930) direct method, I obtained normal figures (unpublished observation). That the capillary pressure is very nearly normal is almost certainly indicated by Govaerts' (1927) observation that the colloidal osmotic pressure of the blood in essential hypertension is but a little higher than normal, for there are good grounds for believing that, if the capillary pressure were much higher than the colloidal osmotic pressure, excessive tissue fluid would be formed (Chapter 4). Thus it would seem very probable that the abnormal resistance in essential hypertension is interposed between arteries of the order of size of the digitals and capillaries, that is to say in the small arteries and arterioles.

THE PULSE PRESSURE

The pulse pressure has been discussed in Chapter 4. It depends on the relationship between the stroke output of the left ventricle and the distensibility of the aorta and its large branches. Since aortic distensibility falls as the pressure inside it is raised, an increase in mean arterial pressure will itself cause an increased pulse pressure. In the absence of factors enumerated on p. 46 as altering stroke output, the chief additional factor determining pulse pressure is the elasticity of the aorta and its large branches, which is partly, at least, a property of age. Thus, in general, for a comparable diastolic pressure, older subjects tend to have higher systolic pressures than young subjects.

THE BLOOD FLOW THROUGH THE VARIOUS ORGANS

Measurement of the blood flow through the various organs of the body is of interest in its own right because the supply of blood is the only function of the circulation, and because of the light which such measurements throw on the distribution of the increased peripheral resistance and, therefore, on the nature of the agent responsible for hypertension.

The first attempts were by Prinzmetal and Wilson (1936) and by Pickering (1936b), who measured the blood flow through the forearm by Hewlett and van Zwaluwenburg's method. Both found similar rates of blood flow in normal subjects and subjects with essential hypertension, at rest and after the dilator stimulus provided by circulatory arrest up to ten minutes duration. In addition, Prinzmetal and Wilson found similar rates of flow in subjects with normal and raised pressures in response to local heat, to warming the body or to

Homer Smith and his school (see Smith, 1951). There is now an impressive body of evidence as to the reliability of the inulin clearance as a measure of glomerular filtration rate, and of the diodone clearance as a gauge of renal blood flow, especially when checked by determining the extraction ratio by catheterization of the renal vein.

By such methods, Goldring, Chasis, Ranges and Smith (1941) investigated the renal circulation in 60 cases of essential hypertension of varying severity up to the terminal malignant phase. A major difficulty in comparing the kidneys in normal and hypertensive subjects is the frequency in the latter of organic vascular disease and its consequences. To surmount this difficulty, inulin and diodone clearances were related to the value for the total amount of functioning tubular tissue, as given by the maximal capacity of the tubules to excrete diodone (Tm_D). Taking the series as a whole, the tubular excretory mass tended to be decreased, being less than the normal mean (51.6 mg. iodine per min.) in all but three patients, and being lowest in subjects with advanced retinopathy and significant proteinuria; in the eight patients with papilloedema, Tm_D was between 3 and 19.8 mg iodine per min. The effective renal blood flow also tended to be reduced, the extremes being 41.7 and 1,179 ml per min. (normal mean 1,275 ml. per min.); in 45 out of 60 cases it was more greatly reduced than the tubular excretory mass, suggesting a relative ischaemia of the residual functioning tubules. Inulin clearance (C_{IX}) was also reduced, but less so than Tm_D , so that the ratio $\frac{C_{IX}}{Tm_D}$ exceeded the mean normal value

They concluded "Since the relative ischemia in these hypertensive subjects is correlated with a rise in filtration fraction . . . that the . . ."

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of "impotent nephrons," that is to say, nephrons whose glomeruli fill but whose tubules do not secrete.

This efferent arteriolar constriction, which thus seemed to be the characteristic feature of the renal circulation, was not thought to be due to action of the sympathetic nervous system.

was lowered, by pyrogenic

that the muscle vessels are either not constricted, or are less constricted than the other vessels in the body, so that at rest the muscles get more than their normal share of blood. Observations on the effect of exercise on muscle blood flow are difficult to make quantitative, but so far as they go, Stead and Kunkel (1940) and Abramson and Fierst have obtained normal flows in hypertension. Wilkins and Eichna (1941b) obtained flows after five minutes circulatory arrest that were larger in subjects with hypertension than in those with normal pressures, the flow being related to the sum of systolic and diastolic pressures. Abramson and Fierst found reactive hyperemia flows that were slightly, but not significantly, greater in hypertensive than in normal subjects.

Brain. Williams and Lennox (1939) found a normal value for O_2 and CO_2 in blood drawn from the internal jugular vein in subjects with hypertension and this is strongly in favour of a normal cerebral blood flow. Using the nitrous oxide method for determining cerebral blood flow, Kety and his colleagues (1948) found similar values in normal subjects and subjects with essential hypertension; further they found (Harmel and others, 1949) that anaesthetization of the stellate ganglion with novocaine produced little change in cerebral blood flow in normal subjects or in subjects with essential hypertension. It seems justifiable to conclude that the cerebral vessels share in the generalized vasoconstriction, that they are narrowed no more and no less than other vessels, and that this narrowing is not the result of overactivity of the sympathetic nerves.

Liver. Circulation through the gut, which eventually passes through the liver, is of special interest in hypertension because of the old idea that hypertension was due primarily to splanchnic vasoconstriction. Using the bromsulfalein extraction method, Culbertson and others (1951) found the liver blood flow of the same order in essential hypertension as in normal subjects. Thus it would seem that here again there is increased vascular resistance which is of the same order as that found elsewhere. Wilkins and others (1951) showed that standing up produced a fall in splanchnic blood flow in normal subjects and subjects with hypertension, which was due to splanchnic vasoconstriction; after splanchnic sympathectomy in subjects with essential hypertension, the fall of hepatic flow on standing could be accounted for by the concomitant fall of arterial pressure without invoking any change in splanchnic vascular diameter. We may conclude from this that the splanchnic vasoconstriction which occurs on standing is, in subjects with essential hypertension as in normal subjects, mediated through the sympathetic nerves.

Kidney. Our knowledge of the circulation through the kidney is largely dependent on the clearance methods perfected and tested by

Homer Smith and his school (see Smith, 1931). There is now an impressive body of evidence as to the reliability of the inulin clearance as a measure of glomerular filtration rate, and of the diodone clearance as a gauge of renal blood flow, especially when checked by determining the extraction ratio by catheterization of the renal vein.

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to the value for the total amount of functioning tubular tissue, as given by the maximal capacity of the tubules to excrete diodone (Tm_D). Taking the series as a whole, the tubular excretory mass tended to be decreased, being less than the normal mean (51.6 mg. iodine per min.) in all but three patients, and being lowest in subjects with advanced retinopathy and significant proteinuria; in the eight patients with papilloedema, Tm_D was between 3 and 19.8 mg. iodine per min. The effective renal blood flow also tended to be reduced, the extremes being 41.7 and 1,179 ml. per min. (normal mean 1,273 ml. per min.); in 45 out of 60 cases it was more greatly reduced than the tubular excretory mass, suggesting a relative ischæmia of the residual functioning tubules. Inulin clearance (C_{IN}) was also reduced, but less so than Tm_D , so that the ratio $\frac{C_{IN}}{Tm_D}$ exceeded the mean normal value

in 43 of 60 subjects and in 21 of these exceeded the mean + twice the standard deviation. The filtration fraction, that is the percentage of glomerular filtrate formed from plasma filtered off by the glomeruli, tends then to be increased above the mean normal value of 19 per cent. They concluded "Since the relative ischæmia in these hypertensive subjects is correlated with a rise in filtration fraction we conclude that the ischæmia

is due to the existence in these subjects of "impotent nephrons," that is to say, nephrons whose glomeruli fill but whose tubules do not secrete.

This efferent constriction, characteristic of essential hypertension, was not thought to be due to action of the renin-angiotensin system, it was found in three subjects after removal of the adrenal glands. Thus the increased efferent tonus in essential hypertension was not caused by a structural obstructive lesion was demonstrated by their observation that the renal blood flow can be increased, and the filtration fraction lowered, by pyrogenic

agents which produce these effects in the normal kidney. They concluded that "the functional picture presented by the hypertensive kidney is consonant with the theory that there is present in the blood in hypertensive disease one or more pressor substances which produce a reversible renal ischemia by constriction of the efferent glomerular arterioles." That this renal ischaemia was effect and not cause of hypertension was, they thought, supported by the observations of Chasis and Redish (1941) that the changes were observed equally in the two kidneys in 21 subjects with essential hypertension selected at random.

It seemed that there were intrinsically two changes in the renal circulation in essential hypertension; first, a reduction in the amount of functioning renal tissue inferred to be progressive and accompanied by a corresponding reduction of renal blood flow; second, a relative ischaemia of the remaining functional tubular tissue due to narrowing of the efferent glomerular arteries. The first of these was the functional counterpart of the organic vascular changes discussed in Chapter 11; so far as has been ascertained, it represents an effect of hypertension rather than its cause. The second represents a functional constriction of non-nervous origin: it affects the two kidneys equally (Chasis and Redish, 1941) and may be presumed to be an expression of the agency responsible for the raised arterial pressure.

Gregory, Levin, Ross and Bennett (1946) studied the effects of spinal anaesthesia in 10 hypertensive patients with anaesthesia up to D3 in all, and with anaesthesia up to the clavicle in two of them. The inulin and diodone clearances fell by similar amounts, and the falls were roughly proportional in extent and duration to the fall of arterial pressure. On the other hand, Corcoran, Taylor and Page (1948) found that, in most instances, spinal anaesthesia to D5 was followed by a rise (average 22 per cent.) in renal blood flow in patients with hypertension, the filtration rate generally decreasing (average 12 per cent.). Since the mean pressure was invariably decreased to levels ranging from 85 to 125 mm., they concluded that a significant proportion of the increased renal vascular resistance is dependent on nerve impulses which are blocked by anaesthesia extending to D5. They concluded that "Qualitatively, the renal vascular responses of normotensive and hypertensive patients to these procedures are identical. Quantitatively, they may differ slightly in that, in hypertension, a fraction of afferent arteriolar resistance is not removed by anaesthesia."

The observations of Goldring, Chasis, Smith and their colleagues seemed to have defined clearly the disturbance of the renal circulation in hypertension. Bolomey and his colleagues (1949) did not perhaps get such clear-cut results, particularly as regards filtration fraction, but as they were estimating cardiac output simultaneously, their

subjects were even less basal. Cargill (1949) measured extraction ratios of inulin and PAH¹ in normal subjects, and patients with pyelonephritis, glomerulonephritis and essential hypertension. He found that a high filtration fraction was characteristic of essential hypertension and a low one of glomerulonephritis. He also showed that PAH extraction fell with PAH clearance, but tended to be higher in essential hypertension than in glomerulonephritis. Finally, Gómez (1951), also of Smith's laboratory, has produced a new set of formulae from which the resistance in the afferent and efferent arterioles and in the venous segment can be calculated. With these he has shown that the chief increase in resistance in the kidney in essential hypertension is not in efferent but in afferent arterioles. He accepts the effects of pyrogens as indicating that this is functional rather than organic.

This rather dramatic volte face from the efferent to the afferent arteriole, given the same set of data, emphasizes clearly to my mind how very precarious all these detailed interpretations of clearances are, since they are all based on unverified simplifications and assumptions. One only has to remember (a) that there is in health some evidence of shunts in the kidney (Pappenheimer, personal communication), (b) that in disease extraction ratio is altered and that there is an extensive reorganization of vascular architecture (Dehoff, 1920; Oliver, 1939) to conclude that these interpretations are no better than inspired guesses. Gómez's formulae are being widely and quite uncritically used to measure not only afferent and efferent tone, but also extraglomerular pressure. The assumptions on which his calculations are based are given fully in his paper. They should be very seriously considered by all who use the formulae.

The Circulation as a Whole

Table 7.1 summarizes figures which I collected in 1943 and revised in 1950, to show how the cardiac output is distributed to the various organs of the body. The figures are only approximately valid, since they were obtained by many different workers in different lands working under rather different conditions. But the figures strongly suggest that despite the considerable rise of pressure in essential hypertension, the various organs of the body receive amounts of blood that are very similar to those in subjects with normal pressure. The abnormal peripheral resistance is thus distributed with remarkable uniformity over the tissues of the body, sparing the muscles a little, and being unusually intense in the kidney. In seeking the cause of this, one must be very careful at any time. It is

... such kinds of agent: over-

¹ PAH = Sodium paraaminohippurate

TABLE 7.1. *Comparison of Rates of Blood Flow through Tissues of Normal Subject and Patient with Essential Hypertension, each having a Body Surface of 1.73 Square Metres (Pickering, Advances in Internal Medicine, 1950, 4, 445).*

	Normal subject ml./min.	Patient with essential hypertension ml./min.
Cardiac output (a)	5,900	5,900
Muscle (b)	800	1,360
Kidney (c)	1,300	800
Liver, including gut (d)	1,400	1,400
Brain (e)	810	810
Other organs (f)	1,590	1,530

Note: The basis of these figures is as follows:

(a) Cardiac output. Normal values given by Lauson, Bradley and Cournand (1944) for determinations by cardiac catheter; the same figure taken for essential hypertension.

(b) Muscle. Abramson and Forst (1942) obtained the following average figures at 32° C. Forearm: normal, 1.77; hypertension, 2.86 ml./100 ml./min. Calf: normal, 1.38; hypertension, 2.38 ml./100 ml./min. Barcroft and Edholm (1945) point out that at bath temperature of 34° C., which preserves normal values for deep

value.

(d) Liver. Figures from Culbertson and others (1947) obtained by clearance of bromsulfalein and hepatic vein catheterization.

(e) Brain. Figures from Kety and others (1948), using the nitrous oxide method and assuming brain weights of 1.5 kg.

(f) Other tissues by subtracting sum of b, c, d, and e from cardiac output.

action of the vasomotor nerves, a humoral agent, and structural vascular change. The evidence for the participation of each of these may now be reviewed briefly.

MECHANISM BY WHICH THE PERIPHERAL RESISTANCE IS INCREASED

The Sympathetic Nerves

Like all obscure disorders of the vascular system, hypertension has been ascribed to overaction of the sympathetic vasomotor nerves. Most of the evidence is of the vaguest kind which is scarcely worth

discussing There are, however, four kinds of evidence that are more definite, namely, the effects of sympathectomy; the temporary effects of interrupting vasomotor nervous impulses on (a) the circulation as a whole and on (b) the individual organs; and the urinary excretion of noradrenaline.

The effects of sympathectomy on the arterial pressure are discussed briefly in Chapter 15. The fact that the majority of patients show a return of arterial pressure to the pre-operative level after the removal of the major part of their paravertebral chains, suggests strongly that hypertension is not simply a manifestation of sympathetic over-activity, though, of course, this does not prove that the sympathetic nerves do not participate in the mechanism raising arterial pressure.

In five cases of essential hypertension, Richards (1945) gives the average cardiac outputs before and after bilateral sympathectomy as 5.70 and 5.52 litres respectively, and the calculated peripheral resistances as 2,250 and 1,960 dynes per cmm. cm^{-3} per sec., the mean arterial pressure having fallen from 160 to 135 mm. Hg. There are, unfortunately no comparable figures for normal subjects.

The effects of spinal anaesthesia were extensively investigated in the hope that they might provide a means of distinguishing between those patients in whom sympathectomy would produce a good fall in blood pressure. In this respect (Pugh, 1948). Pugh (1948) found that in 10 control and nine

hypertensive subjects in whom anaesthesia was carried to the level of the fourth to sixth thoracic segments. A fall of blood pressure occurred in all cases, mainly attributable to a fall in cardiac output. Although peripheral resistance also fell, any difference was too slight to be demonstrated convincingly by the methods used.

Effects of Interrupting Sympathetic Impulses on Organ Blood Flow
As we have seen, temporary interruption of sympathetic impulses to hand and brain leaves an abnormal vascular narrowing which is enough to counteract the effect of raised arterial pressure on blood flow. In the kidney, increased vascular resistance persists after splanchnic section and upper abdominal sympathetic ganglionectomy. In the liver, blood flow, with the patient horizontal, increases after sympathectomy, but there are no comparable figures for normals. As for muscle, Wilkins and Eichna's (1941a) measurements on the calf, though not specifically designed to answer the question, revealed blood flows that were not abnormally large after sympathectomy. It would seem probable, therefore, that in essential hypertension an agent exists which causes increased vascular resistance in several tissues independently of the sympathetic nerves.

The Urinary Excretion of Noradrenaline. As will be discussed

more fully in Chapter 20, Von Euler and his co-workers have shown that between 2 and 4 per cent. of infused noradrenaline is excreted in the urine; adrenalectomy does not affect the excretion though it greatly reduces that of adrenaline. It would seem, therefore, that most of the noradrenaline normally excreted arises from the vasomotor nerve-endings. V. Euler, Hellner and Purkhold (1954) found noradrenaline excretion within normal limits in 66 per cent. of 500 cases of essential hypertension, but elevated in the remainder. However, it is still uncertain whether this is a phenomenon of ageing (see p. 409) or can be regarded as evidence for unusual sympathetic activity in these cases.

Humoral Agents

One of the difficulties in looking for a humoral agent in hypertension is that, its chemical properties being unknown, there is no certain way of extracting it. Transfusion of fresh whole blood from subjects with hypertension produces no greater rise of pressure in anæmic recipients than does normal blood, even when 600 ml. is transfused in six minutes (Pickering, 1936a), or when 2,300 ml. is exchanged (Prinzmetal, Friedman and Rosenthal, 1936). A very large number of papers has been published alleging that extracts of blood from patients with hypertension have abnormal vaso-active properties. Most of these are not well controlled, have not been confirmed and will not be reviewed here. Instead, attention will be devoted to the rôle, if any, of those pressor substances whose existence in the body is well authenticated.

Adrenaline and Noradrenaline. I have never had much doubt that adrenaline is not the agent concerned in producing essential hypertension, since its effect on the circulation (see Chapter 4) is so different from the pattern found in essential hypertension. Moreover, the intravenous injection of a very small dose of adrenaline (2 μ g.), barely sufficient to raise arterial pressure, blanches the normally red face of a patient with essential or chronic hypertension (Pickering and Kissin, 1936). Noradrenaline is a much more probable agent, but this also blanches the skin, a feature conspicuously developed in the paroxysms of phæochromocytoma, but notably absent in benign essential hypertension. It seems that the urinary excretion of adrenaline is within normal limits in most cases of essential hypertension. Noradrenaline excretion is normal in most, but as we have seen it may be elevated in some, possibly reflecting in those an increased activity of the vasomotor nerves.

Pitressin. Theobald (1934) has pointed out that pitressin is a feeble pressor substance but a powerful anti-diuretic in man. In minute doses it also produces intense blanching of the human skin.

its action clearly fails to reproduce the known state of the circ-

are, superficially at least, not unlike the pattern found in essential hypertension. Moreover, the idea that essential hypertension was due to release of renin by the kidney harmonized with the similarity between essential hypertension and those forms of persistent hypertension associated with chronic renal disease, the similarities between essential hypertension and experimental renal hypertension, and the frequency of arterial and arteriolar lesions in the kidney in essential hypertension. The hypothesis will be found developed by Goldblatt (1951), Braun-Menendez and others (1946) and Pickering (1943). It seemed to find strong support in the finding of Goldblatt (1951) that

pressor pressures, except for the kidney, which was by far the commonest site in those with elevated, and one of the least common in those with normal, pressures. The hypothesis has now passed out of favour and for two reasons. In the first place, there is a good deal of evidence (see Bell, 1951) that subjects in the early phases of essential hypertension, that is to say, young subjects with moderate hypertension, may show no abnormalities in the renal arteries and arterioles *post mortem*. Secondly, no one has yet succeeded in demonstrating an abnormal amount of renin in human hypertension. Thus Landis (1941) was unable to detect abnormal amounts of renin in kidneys from patients dying of benign hypertension or glomerulonephritis, but did so in four of fourteen kidneys from malignant hypertension. Haynes, Dexter and Seibel (1947) obtained blood from the renal vein by catheter, and assayed the renin content by the method of Leloir and others (1940), renin was detected in approximately the same amount and with the same frequency in a group of 12 patients with varying types of hypertension¹ and in a group of 12 patients with normal

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cardiac failure. In cardiac failure, *unlike* is also some evidence of efferent glomerular arteriolar constriction, and if, in this condition, renin is released in amounts detectable by present methods but

¹ Essential hypertension, 2, malignant hypertension, 2, chronic pyelo-nephritis, 2, chronic nephritis, 2, acute nephritis, 1, coarctation of aorta, 1; nephrotic syndrome, 1; unilateral renal disease, 1.

insufficient to produce hypertension, then it is difficult to believe that renin can be responsible for essential hypertension or, indeed, for other forms of persistent hypertension, and yet be present in amounts too small to detect. It is to be noted, however, that methods of assay are so imperfect that no conclusions are yet possible.

While the general hypothesis that essential hypertension is due to a renal disturbance, and the particular hypothesis that it is due to renin are unsubstantiated, it seems wise to preserve an open mind. Until we understand the mechanism of hypertension produced by renal artery constriction, it is not surprising that we do not understand that occurring naturally in man.

Adrenal Cortical Secretions and Electrolytes

That the adrenal cortex may be concerned in the pathogenesis of essential hypertension was suggested by three observations: (a) that when large doses of DCA and salt were given to patients with Addison's disease, a considerable rise of pressure, even to hypertensive levels, might result (Thorn and Firor, 1940; McCullagh and Ryan, 1940); (b) that when a patient with hypertension developed Addison's disease, his blood pressure fell to normal limits and was restored by DCA (Thorn and others, 1952); (c) that hypotension is a characteristic finding in Cushing's disease, which may be a manifestation of an adrenal cortical tumour, and, in such instances, may be relieved by excising the tumour. Again the adrenal steroids have been shown to be necessary for the genesis of hypertension following renal artery constriction, and possibly for that following nephrectomy (Chapter 5). Finally, in certain animals, hypertension can be induced by large doses of adrenal cortical steroids, if salt is included in the diet, or by salt alone (Chapter 5).

It is at present far from clear how the adrenal corticoids raise arterial pressure. In general, DCA produces much more renal retention of sodium and excretion of potassium, and has a much greater effect on arterial pressure, than has cortisone. It has, therefore, been supposed that the hypertension is due to some kind of electrolyte disturbance. That it cannot be due to simple retention of sodium and chloride is shown by the absence of hypertension in the nephrotic syndrome and in cirrhosis of the liver with ascites, in both of which sodium retention is gross and in which there is some evidence (Luetscher and Johnson, 1953) of an increased urinary secretion of the aldosterone fraction of the adrenal corticosteroids.

It has, therefore, been supposed that an alteration in the intracellular ratio of sodium to potassium may be concerned, but this has not been substantiated.

The possibility that essential hypertension may be due to increased

secretion, or altered pattern of secretion, of adrenal steroids will undoubtedly be put to the test in the next few years, as methods for the separation and assay of these hormones are developed and perfected. It has been reported (Luetscher and Deming, 1951) that the urinary secretion of sodium retaining lipid activity is increased in hypertension, but since it appears also to be in nephrosis, the relevance of the observation is not clear. It will be seen in Chapter 16 that patients with advanced hypertensive disease in whom both adrenals have been removed and in whom minimal supporting therapy of cortisone or DCA and salt is given may retain their hypertension unchanged. Such patients may be contrasted with patients in whom both adrenals have been removed for carcinoma, in whom similar supportive therapy is given, and in whom hypertension was initially and subsequently absent (Huggins and Scott, 1945). Such a contrast would seem to make it quite certain that the hypertension is not due simply to adrenal disfunction. In view, however, of the generalization presented in this work that hypertension may persist when the initial cause has been removed, it would be unwise to go further; it is obviously still possible that a cortical disturbance, now past, might have initiated the change.

Thorn and his colleagues (1952) remark of their patients in whom both adrenals had been removed for hypertension: "In those patients whose blood pressure has fallen in response to adrenalectomy it has been possible to restore the blood pressure toward the original hypertensive levels with desoxycorticosterone, occasionally even with small doses such as 2.5 mg daily, or large supplements of sodium chloride (8 to 9 gm. daily), administered for only a few days, and in one patient in whom an adequate trial of corticosterone was administered a similar response was observed." Lukens (1953) recorded similar findings. Those results recall the observation by Knowlton and others (1946) that 2.5 mg. DCA administered daily to normal rats produced only a slight rise of blood pressure, but given to rats with nephrotoxic nephritis produced a gross hypertension. Those effects were dependent on the presence of sodium chloride in the diet and were not affected by the administration of potassium (Knowlton and others, 1947). Perera and Blood (1947a) found that the subcutaneous injection of 5 mg. DCA twice daily for one week produced a rise in blood pressure in 10 out of 14 subjects. In 14 subjects, definite rises

The prompt rise in blood pressure in the hypertensive group could not be ascribed to salt and water retention, as there were similar changes in the normal group.

The possibility that a sodium disturbance is related to essential hypertension is made plausible by the fall of arterial pressure that may

occur on a diet containing 250 mg. Na daily or less (see Chapter 15). Moreover, Perera and Blood (1947b) showed that increase in dietary sodium chloride from 4 gm. to 15 gm. produced a slight but definite rise in arterial pressure in six patients with hypertension and that salt was necessary for the DCA effect already noted. Further, Perera and Blood (1946) found that when sodium is completely withdrawn from the diet, for twenty-four hours, a normal subject continues to lose sodium and loses weight, whereas in patients with essential hypertension, sodium is not excreted and weight is not lost. Finally, Farnsworth (1946) has shown that when $\frac{U^1}{P}$ chloride is plotted against $\frac{U}{P}$

inulin the result is a straight line for a normal subject or group of normal subjects, with the theoretical implication that if no water were absorbed by the tubule, all the chloride would be reabsorbed. The results for a similar group of subjects with essential hypertension have a different scatter, indicating that the tubular reabsorption of chloride is impaired in hypertension.

The implications of these observations are far from clear. That the kidney in a subject with essential hypertension deals with sodium and chloride rather differently from normal seems however established.

Organic or Structural Changes in the Vessels

The changes in vascular structure occurring in association with raised arterial pressure are described in Chapter 11. Changes in distensibility of the aorta and its main branches affect the pulse pressure, but should not increase the peripheral resistance. Here we are chiefly concerned with changes in the small arteries and arterioles, namely medial hypertrophy, elastosis, intimal proliferation, fatty hyaline intimal thickening and the acute necroses of the malignant phase.

There would seem little doubt that these organic changes, which encroach on the lumen of small arteries and arterioles, must contribute to the increased peripheral resistance. But the consensus of current opinion is opposed to their being entirely responsible for the increased peripheral resistance, for two reasons which may now be examined.

The first reason given is that the increased peripheral resistance in hypertension may be diminished by certain vasodilator agents. Thus it will be shown later in this chapter that the fall in arterial pressure produced by the intravenous injection of histamine is greater in subjects with essential hypertension than in normal subjects. The same seems to be true in the pyrogenic reactions. The vasodilatation in the forearm vessels in reactive hyperæmia is at least as great, and

¹ $\frac{U}{P}$ is the ratio of the concentration of a substance in the urine (U) and plasma (P).

peripheral resistance in essential hypertension, are, in most instances, capable of dilatation. But it is not clear to the writer, who is responsible for some of this evidence, that any of these observations prove that the "abnormal" constituent has been removed.

The second and more formidable reason is that these structural lesions are too slight and too inconstant to constitute the whole abnormality in vascular behaviour which is observed. Thus these organic changes are mainly absent from muscle and skin and comparatively slight in brain and gut. They are pronounced in kidney where they are the basis of important changes in renal structure and function. Even here, there is some evidence that the abnormal constriction, be it of the afferent or efferent arterioles, is functional and not organic, since it is relaxed by pyrogens.

VASCULAR REFLEXES AND VASCULAR RESPONSES IN ESSENTIAL HYPERTENSION

The Carotid Sinus Reflex

After the discovery of the carotid sinus reflex, and the demonstration that high blood pressure could be produced by section of the carotid sinus and depressor nerves, it was natural that the hypothesis should be held that essential hypertension was due to an interference with these reflexes. Regniers (1930) and Mies (1932) both described patients in whom pressure on the carotid sinus produced a fall of arterial pressure, while digital obliteration of both carotids below the sinuses gave no response. These observations were repeated by Gammon (1936) and by Pickering, Kissin and Rothschild (1936), who both found the carotid sinus mechanism active in essential hypertension. We found that digital pressure on the sinus produced falls of pulse rate and blood pressure (expressed as percentage of initial) of 1.7 and 2.6 in young normal, 6.7 and 6.2 in chronic nephritis, 10.1 and 8.2 in elderly normal and 12.0 and 10.3 in essential hypertension. Thus the response, both in terms of blood pressure and pulse rate, was

the same side. In order to make sure that the changes in pulse rate and blood pressure were due to stimulation of the sinus, we also recorded the effects of (a) similar pressure on the neck avoiding the carotid, and (b) compression of one femoral artery. In each patient

tested, the rise in blood pressure and pulse produced by carotid compression was greater than the sum of the other two. Taking the series as a whole, there was no clear difference between the sizes of response in young or elderly subjects with "normal" blood pressure, and patients with chronic nephritis or essential hypertension. In two of the seven patients with essential hypertension and three of the four patients with chronic nephritis with hypertension, release of carotid compression gave a fall of arterial pressure, a slowing of the pulse, or both. It is clear, then, that the carotid sinus mechanism remains active in some cases, at least, of essential hypertension.

The really important point, whether the reflexes are excited to the same extent, or to a greater or less extent, in essential hypertension than in subjects with lower pressures, can, however, not be decided by experiments as crude as this. Obviously, it would be expected that unless some adaptation has occurred either in the baro-receptors or in the central connections, the discharge down the efferent limbs of the arc would be much increased in essential hypertension. The normal pulse rate and the responses to carotid compression below the sinus suggests that it is not. Could this adaptation, if indeed it has occurred, have something to do with the maintenance of an elevated arterial pressure? Could the homeostatic reflex mechanisms be set at a new and higher level which these reflexes sustain, just as they sustain the pressure at a lower level in normal subjects?

Venesection

Miller (1926), avoiding the psychic factor, found the maximum reduction in blood pressure only 15 mm. Hg after removing 500 ml. blood from four patients with hypertension

Postural Reflexes

When a normal subject is tilted from the horizontal to the upright posture, the arterial pressure at heart level remains unchanged, and there is simultaneously vasodilatation in the head and vasoconstriction in the lower part of the body. In subjects with essential hypertension, the arterial pressure also remains unchanged with this change of posture and there is some further evidence that the homeostatic mechanism effecting these adjustments is intact. Culbertson and others (1951) found that the decrease in hepatic blood flow produced by tilting into the upright (75°) position was approximately the same in eight subjects with normal pressure and 12 with essential hypertension. These changes do not occur after sympathectomy. Similarly, Hafkenschiel and others (1951) found that tilting to the 20° head-up position produced the following percentage changes respectively in normal subjects, subjects with essential hypertension, and hypertensive

subjects after splanchnic sympathectomy: in "effective" mean arterial pressure: -17 per cent., -16 per cent. and -26 per cent.; in cerebral blood flow: $+2$ per cent., -5 per cent. and -11 per cent.; and in cerebral vascular resistance: -18 per cent., -15 per cent. and -17 per cent.

The very clear similarity in behaviour between splanchnic and cerebral circulations in response to change in posture suggests that the homeostatic mechanisms play very much the same part in maintaining the arterial pressure at a high, as they do at a low, level. To the writer this would seem a most important conclusion, worthy of more detailed and deliberate study.

"Cold Pressor" Test

Hines and Brown (1933) measured the rise in blood pressure that occurs in response to immersing the hand in water at 4°C . and obtained the following mean responses of systolic and diastolic pressure. (a) 8.9 mm and 7.5 mm. Hg in 40 normal subjects aged 17 to 50 years; (b) 30.1 and 21.1 mm. Hg in eight subjects with "potential hypertension" aged 19 to 44 years with normal blood pressure but with a family history of hypertension; (c) 32 and 21 mm. in seven cases of early or labile hypertension without retinal sclerosis or cardiac enlargement; (d) 38.4 and 32.5 mm. in 11 cases of hypertension with retinal sclerosis and enlarged heart; (e) 13.1 and 10.8 mm. in eight patients aged 55 to 91 with arteriosclerosis but without hypertension. They therefore claimed that a hyper reactive vasomotor system was characteristic not only of essential hypertension but of those destined to develop it. Pickering and Kisson (1936) failed, in the main, to confirm these observations in a small series, finding mean rises of 8 and 6 mm. in young control subjects, mean age 33 years; 22 and 11 mm. in old control subjects, mean age 53 years; 17 and 9 mm. in chronic nephritis, mean age 40 years; and 21 and 13 mm. in essential hypertension, mean age 54 years. They concluded that the rise of blood pressure produced in this test is greater in older than in young subjects and that its size seems to be related to the discomfort the subject experiences, but is largely independent of the resting blood pressure. Alam and Smirk (1938) agreed that the size of response increased with age, but found larger responses in essential than in renal hypertension. While the responses were in general larger in essential hypertension than in normal subjects, they sometimes found large rises of blood pressure in normal subjects and small rises in subjects with essential hypertension.

A very large literature has grown up on this test, since it was at one time thought that it was indicative of overaction of the

tested, the rise in blood pressure and pulse produced by carotid compression was greater than the sum of the other two. Taking the series as a whole, there was no clear difference between the sizes of response in young or elderly subjects with "normal" blood pressure, and patients with chronic nephritis or essential hypertension. In two of the seven patients with essential hypertension and three of the four patients with chronic nephritis with hypertension, release of carotid compression gave a fall of arterial pressure, a slowing of the pulse, or both. It is clear, then, that the carotid sinus mechanism remains active in some cases, at least, of essential hypertension.

The really important point, whether the reflexes are excited to the same extent, or to a greater or less extent, in essential hypertension than in subjects with lower pressures, can, however, not be decided by experiments as crude as this. Obviously, it would be expected that unless some adaptation has occurred either in the baro-receptors or in the central connections, the discharge down the efferent limbs of the arc would be much increased in essential hypertension. The normal pulse rate and the responses to carotid compression below the sinus suggests that it is not. Could this adaptation, if indeed it has occurred, have something to do with the maintenance of an elevated arterial pressure? Could the homeostatic reflex mechanisms be set at a new and higher level which these reflexes sustain, just as they sustain the pressure at a lower level in normal subjects?

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we feel that the magnitude of hyperemia obtained in the hypertensive subjects is equal to that obtained in normals."

They also showed (Chasis and others, 1942) that repeated injections of pyrogenic material (pyrogenic inulin, triple typhoid vaccine, tyrosinase) would reduce the arterial pressure significantly in subjects with essential hypertension and that the arterial pressure can be kept at reduced levels by repeated injections. This hypotensive effect can be obtained without a rise in body temperature by premedication with amidopyrine.

Bradley and others (1945) have compared in greater detail the response to pyrogens in two normal and six hypertensive subjects, fever being prevented by amidopyrine. In all subjects cardiac output increased as a result of an increase in both pulse rate and stroke volume, while total peripheral resistance decreased. The arterial pressure fell in

that the head had to be lowered to maintain the arterial pressure at an adequate level. Change to the upright posture produced no symptoms in normal subjects, but symptoms of cerebral ischaemia in those with essential hypertension, symptoms attributed to a fall in cardiac output

While the responses to pyrogens are in the main closely similar in subjects with normal pressures and essential hypertension, it is still uncertain whether they are quantitatively the same, since casual observation suggests that the falls of arterial pressure tend to be considerably greater in subjects with essential hypertension

Other Responses of the Circulation

A very large number of papers have been published alleging that the change in arterial pressure induced by certain agents is abnormal in patients with essential hypertension. An inherent difficulty is to compare responses when the initial values differ. Should one, for example, express the rise or fall in mm. Hg or as a percentage of the initial value? Thus Pickering, Kisson and Rothschild (1936) injecting 0.1 mg histamine acid phosphate intravenously obtained the following average falls of systolic and diastolic pressure:

- (a) 27 and 19 mm in six control subjects, aged 29 to 60 years, with average initial pressures 118 and 73 mm. Hg.
- (b) 49 and 24 mm in four patients with chronic nephritis, aged 17 to 48, with average initial pressures 195 and 110 mm. Hg.
- (c) 59 and 31 mm in five patients with essential hypertension, aged 41 to 64 years, with average initial pressures 226 and 126 mm. Hg.

pathetic nerves and would pick those patients who would respond well to sympathectomy, a hope that has not been fulfilled. It is extremely doubtful what this test means, and in view of the undoubted fact that the large responses are not confined to patients with essential hypertension or small responses to those with "normal" pressures, it seems profitless to pursue it further. The subject is reviewed by Wolff (1951) who emphasizes the relationship between pain and rise of pressure.

Body Temperature Control

Body temperature is regulated by adjustment of heat production and heat loss. In the latter, the circulation through the skin is of primary importance, being regulated by reflexes from peripheral and central receptors, effected through the sympathetic vasomotor nerves. General experience suggests that body temperature is controlled about as closely, and by the same mechanisms in subjects with essential hypertension as in normal subjects. The writer observed that the vasodilatation in the hand produced by raising blood temperature proceeded in very much the same way as in normal subjects (Pickering, 1936b).

Fever

It has long been known that in patients with essential hypertension the arterial pressure may fall to "normal" levels during febrile illness such as pneumonia (Volhard, 1931). I have seen this repeatedly. Smith and his colleagues in the course of their work on renal clearances noted that, with the fever accompanying the use of a pyrogenic sample of inulin, the renal blood flow was greatly increased in normal subjects. They showed (Chasis and others, 1938) that in normal subjects during the chill following the injection of a pyrogen, arterial pressure rises, renal plasma flow is decreased and the filtration fraction increased, indicating efferent arteriolar constriction. Later, the blood pressure starts to fall, renal plasma flow rises to values much higher than normal, and filtration fraction falls to subnormal levels, indicating vasodilatation affecting the efferent glomerular arterioles particularly. That qualitatively similar changes occurred in subjects with essential hypertension was shown by Goldring and others (1941), who stated: "Normal subjects vary considerably in sensitivity to pyrogen and this is doubtless true of hypertensive subjects. . . . In the latter $\frac{C_D}{T_{mD}}$ during hyperemia ranges from 17.5 to 34.7 and averages 22.8, figures which are comparable with those . . . on a smaller series of normals in which hyperemia was induced; consequently,

is the presenting sign. It would seem important that we should view the problem, not only from the point of view of physiology, but taking into account all that we have learned from the natural history and from experimental work in animals.

Taking first the physiological approach, we have seen :

(1) That the cardiac output and the fractions of it delivered to the various tissues of the body are very similar in subjects with high and with lower pressures.

(2) That the arterial pressure is regulated in very much the same way, and in many cases with a not grossly dissimilar precision, in those with high and those with lower pressures.

In fact, it would seem that the circulation is carried out in precisely the same way as in ordinary folk but at a higher level of arterial pressure

We have seen further that high arterial pressure does not seem to be due to vasoconstriction of vasomotor nervous origin. Nor, in spite of diligent search, has a humoral cause of vasoconstriction been identified. Intimal thickening of small arteries and arterioles may be a contributory cause for increased peripheral resistance, but its patchy distribution unfits it for being the sole, or even the major, cause.

Such is the conventional analysis, leading, as we have seen, to an impasse. It seems, indeed, probable that what we are seeking is neither nervous or humoral vasoconstriction nor arteriolar intimal thickening. We may turn to the broader approach of the natural history of the condition.

It will be shown later in this work that there is no sharp division between the lower pressures that are conventionally called normal and the higher pressures that are called pathological. The distribution is, in fact, continuous. Arterial pressure tends to rise with age. Arterial pressure is in part determined by genetic factors, and, so far as inheritance is concerned, arterial pressure tends to behave as a graded characteristic (Chapter 3).

Age and inheritance are the only factors determining arterial pressure in the population at large, whose magnitude are as yet assessed, even though this assessment is as yet a most imperfect one. It seems extremely probable that environmental factors are of even greater importance, though their nature and the magnitude of their effects has not yet been, even approximately, defined. But a most important, and seemingly relevant, fact has emerged from a study of both experimental and human hypertension, namely, that when the hypertension has been produced by a specific abnormality, removing that abnormality does not always abolish the hypertension, if this has existed long enough. This was first shown for hypertension produced in the rabbit by constricting the renal artery to the single remaining kidney ;

Expressed as percentages of initial pressure, the falls of systolic and diastolic pressure were 23 per cent. and 26 per cent. in normal subjects, 25 per cent. and 21.5 per cent. in chronic nephritis and 26 per cent. and 24.5 per cent. in essential hypertension.

Deicke and Hulse (1924) claimed that, in contrast to benign hypertension, patients with nephritic hypertension reacted unusually profoundly to adrenaline injected intravenously, and this was used as evidence for his chemical theory of pale hypertension by Volhard (1931). Pickering and Kissin (1936) were unable to confirm this. They showed that the response to 5 μ g. adrenaline was biphasic, a fall followed by a rise. The rises in systolic and diastolic pressure averaged 8 and 6 mm. in seven subjects with normal pressure, 13 and 3 mm. in six patients with chronic nephritis, and 14 and 5 mm. Hg in eight patients with essential hypertension. Gordon and Levitt (1935) found the minimal dose of adrenaline producing a change in arterial pressure was no less in nephritis than in essential hypertension.

Raab (1929) concluded that patients with essential hypertension, unlike those with nephritic hypertension, responded by an unusually big fall of arterial pressure to overbreathing, and regarded this as evidence for hypertension being due to stimulation of the vasomotor centre by CO₂. However, Raab's own results, those of Proger and Ayman (1933) and those obtained by us (Pickering, 1936b) show depressor responses occurring rather irregularly amongst both clinical types.

The response of the cardiovascular system to "stressful" interviews has been studied by Wolff (1953) in both normal subjects and subjects with essential hypertension. In both instances the arterial pressure rose, due sometimes to increases in cardiac output and sometimes to increased peripheral resistance, the latter being the more usual response in essential hypertension; in both groups effective renal blood flow fell more than glomerular filtration rate, so that the filtration fraction increased.

Many other responses have been studied. The degree of variability over the twenty-four hours has been supposed to indicate the size of the neurogenic component. However, if this variability is related to initial pressure it is not particularly large (see p. 166). Again, the size of the response to amytal or other sedative has been supposed to be a measure of the neurogenic component. The fall of pressure is, however, due both to decreased cardiac output and peripheral resistance and the interpretation of the responses is difficult.

COMMENT

The problem that has been discussed in this chapter is quite fundamental to our theme, for we are seeking to define the nature of that peculiarity of vascular behaviour of which raised arterial pressure

tension is a single discrete clinical entity, produced by a single genetic or environmental cause, is almost certainly wrong ; its ætiology is more probably polyphyletic. Similarly, it may be suspected that the high arterial pressure itself is not the resultant of a single vascular fault, but of a series of faults existing in different combinations in different subjects. Perhaps in the far distant future the ingenuity of our successors will have devised methods for identifying and measuring these several faults.

if the hypertension has lasted long enough, removal of the kidney, and even, in some animals, of the clamp, does not reverse the hypertension. In man when there is apparently an abnormality of only one kidney, removing that kidney reduces the pressure substantially in about half the cases, but then not to the expected norm for that age, while in the remainder the pressure is unaltered (Chapter 17). Again, in a substantial number of patients with sustained hypertension associated with a phæochromocytoma, removal of the tumour is not followed by an appreciable fall of arterial pressure (Chapter 20). Finally, where a coarctation of the aorta is repaired, the arterial pressure remains high in the majority (Chapter 22).

The vascular peculiarity for which we are looking would thus seem to have these additional attributes :

- (a) It is probably a quantitative rather than a qualitative departure from the "normal."
- (b) It is in part genetically determined.
- (c) It develops as age advances.
- (d) It is provoked by previous hypertension.

It would seem to the writer that these attributes might well belong to some physical characteristic of the small arteries and arterioles. Moreover, this is the very kind of characteristic that is overlooked by the conventional analysis. The following would seem the chief possibilities which might exist either separately or in combination :

- (1) Muscular hypertrophy of small arteries and arterioles. Subjected to the usual stimuli, the contraction might be greater.
- (2) Increase in length of small arteries and arterioles. If the arterioles in which the chief fall of pressure occurs are of the same average diameter but of unequal lengths, the arterial pressure will vary directly as arteriolar length.
- (3) Altered elastic properties of small arteries and arterioles, so that they tend to be less distensible by the pulse wave.

Of these, the first is known to occur but its influence is unknown ; the second has never, to the writer's knowledge, been investigated¹ ; the third was postulated by Volhard (1931) but has never been investigated and it is not at the moment clear to me how this could be done.

One final comment may be made. Those of us who have sought to identify and measure the basic fault in essential hypertension have in general proceeded on the assumption that there is a single fault. It will be shown later in this book that the view that essential hyper-

¹ It would not seem impossible to do so. It is possible to inject vessels with resins and latex and dissolve the tissue, leaving the injected vessels to be dissected and measured as Oliver has dissected and measured the nephrons of the kidney.

obvious cause for the raised pressure. In 1913 he regarded pressures of 160 mm. Hg as pathological and was inclined to think that 150 mm. Hg would in the end prove a better limit. Lauder Brunton (1909) gave figures of 125 to 135 or 140 mm. Hg as round pressures for men in middle life, and pressures above 150 as abnormal. In 1915 Janeway stated. "I am inclined to revise my former opinion and to agree with Cook, and Lauder Brunton before him, that over 135 mm. up to middle life, and 145 or 150 mm. thereafter, should be regarded as pathological hypertension if found on repeated examinations." The expectation that arterial pressure would prove helpful in assessing life expectation was borne out by the figures of insurance companies which began to accumulate from about 1910. Early figures showed that in young adults low arterial pressures carried an unfavourable prognosis usually from pulmonary tuberculosis, while high figures were accompanied by increased mortality from cardiovascular and renal disease. Thus the desirability of fixing normal limits and the importance of detecting hypotension and hypertension was confirmed. Meanwhile the insurance companies were piling up great quantities of figures concerning the actual arterial pressures recorded at examination of the subjects who had been accepted for life policies. Since no follow-up records were kept of those rejected because, amongst other things, they had arterial pressures above the normal range, it is not surprising that the figures obtained supported, and in fact still further defined, the normal limits of arterial pressure. These figures and those obtained on healthy young men and women formed the basis for the normal figures which were quoted in every text-book of physiology and medicine.

The first seriously to question these pronouncements on normality and abnormality was Alvarez (1919), after taking the blood pressures on 265 men called up as a second draft for service in the closing stages of World War I. He realized that the unexpectedly high incidence of hypertension in this series might be explained by its being a selected sample rejected for service on routine examination. He noted that all other series, on which normal figures were based, were also selected samples, such as aviation recruits, soldiers and particularly the accepted risks of insurance companies. He therefore (1923) carefully analysed the pressures of 6,000 men and 8,934 women entrants to the University of California, whose arterial pressures had been measured as a routine on entry. He noted the wide distribution of pressures, their means and the shape of the distribution curves. He found that for men the systolic pressures were grouped around 127 at age 16, and 118 at age 30, while those for women were grouped about 118 at age 16, and 117 at age 40. Similar observations were made in the University of Minnesota by Diehl and Sutherland (1925) and Boynton and Todd (1947). Boynton and Todd's figures were obtained on 43,800 men and 31,458

CHAPTER 8

THE ARTERIAL PRESSURE IN THE POPULATION AT LARGE AND ITS RELATIONSHIP TO AGE: A CONSIDERATION OF "NORMAL" AND "HIGH" BLOOD PRESSURE

MEASUREMENT of the arterial pressure, with any approximation to accuracy, dates from the instruments of Riva-Rocci (1896) and Hill and Barnard (1897), subsequently improved by the wide cuff introduced by Von Recklinghausen. From the outset, information concerning the behaviour of arterial pressure in the population at large has been obscured by an understandable obsession of practising doctors with the desirability of defining normal and abnormal values. It quickly became apparent that high pressures were more commonly found in older than in young subjects, and a rough guide to the expected systolic level (in mm. Hg) was formulated as $100 + \text{age}$ in years. However, the question arose: was this tendency of arterial pressure to rise with age physiological or pathological; or, in other words, was the rise with age due to increasing incidence of abnormal values? The experience of the nineteenth century when arterial pressure was usually gauged by the compressing finger or a sphygmogram, or by instruments whose accuracy was little greater, had stressed the relationship between raised arterial tension and kidney disease on the one hand and arterial disease on the other. The physician was much concerned with the detection of the pre-albuminuric stage of Bright's disease or the pre-arteriosclerotic stage of arteriosclerosis. These higher pressures might represent, then, early stages of disease, and it seemed important that their possible prognostic significance should not be overlooked. Looked at from the vantage of forty years later, it is doubtful whether this recognition was of positive value to the patient, since his physician could do little for him but make his life a torment. But it was, of course, of the utmost importance to insurance companies; for cardiovascular and renal diseases comprised some of the major causes of untimely death and thus loss of revenue. Pronouncements by men of the standing of Janeway in the United States and Lauder Brunton in Great Britain concerning the upper limits for normal pressure thus fell on extremely fertile soil. Janeway was much influenced by observing that the systolic pressure seldom exceeded 145 mm. Hg in 200 cases, except when there was an

obvious cause for the raised pressure. In 1913 he regarded pressures of 160 mm. Hg as pathological and was inclined to think that 150 mm. Hg would in the end prove a better limit. Lauder Brunton (1909) gave figures of 125 to 135 or 140 mm. Hg as round pressures for men in middle life, and pressures above 150 as abnormal. In 1915 Janeway stated: "I am inclined to revise my former opinion and to agree with Cook, and Lauder Brunton before him, that over 135 mm. up to middle life, and 145 or 150 mm. thereafter, should be regarded as pathological hypertension if found on repeated examinations" The expectation that arterial pressure would prove helpful in assessing life expectation was borne out by the figures of insurance companies which began to accumulate from about 1910. Early figures showed that in young adults low arterial pressures carried an unfavourable prognosis usually from pulmonary tuberculosis, while high figures were accompanied by increased mortality from cardiovascular and renal disease. Thus the desirability of fixing normal limits and the importance of detecting hypotension and hypertension was confirmed. Meanwhile the insurance companies were piling up great quantities of figures concerning the actual arterial pressures recorded at examination of the subjects who had been accepted for life policies. Since no follow-up records were kept of those rejected because, amongst other things, they had arterial pressures above the normal range, it is not surprising that the figures obtained supported, and in fact still further defined, the normal limits of arterial pressure. These figures and those obtained on healthy young men and women formed the basis for the normal figures which were quoted in every text-book of physiology and medicine.

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women examined by the Student Health Service, most of whom were under 26 years of age; but there were over 280 in each five-year age group to 40 years. In men they also noted peak values (mean 123) around age 20, and no tendency for systolic pressure to rise with age. In females systolic pressure showed a steady rise with age from 107 at age 16 to 123 at age 41 and over. Diastolic pressures rose with age in both sexes, the means in men from 72.2 at age 16 to 81.4 at 41 and over and in women from 67.3 to 79.4 at corresponding ages.

A more complete age range was studied by Saller (1928), who analysed the blood pressures of 4,211 patients attending the medical

TABLE 8.1. *Systolic and Diastolic Blood Pressure Readings by Sex and Age (Master, Dublin and Marks, 1950).*

Sex and Age	Systolic			Diastolic		
	Mean	Stand. Dev.	Coef. of Variation	Mean	Stand. Dev.	Coef. of Variation
Males						
16. . .	118.4	12.17	10.28	72.0	10.33	14.17
17. . .	121.0	12.88	10.64	74.4	9.36	12.58
18. . .	119.8	11.95	9.97	74.4	10.03	13.48
19. . .	121.8	14.99	12.31	74.6	10.29	13.79
20-24 . .	122.0	13.74	11.18	76.0	9.93	13.07
25-29 . .	125.1	12.58	10.06	77.8	8.98	11.54
30-34 . .	126.1	13.61	10.79	78.5	9.68	12.33
35-39 . .	127.1	14.20	11.17	80.4	10.42	12.96
40-44 . .	129.0	15.07	11.68	81.2	9.53	11.74
45-49 . .	130.0	16.93	13.02	82.0	10.81	13.18
50-54 . .	134.5	19.21	14.28	83.4	11.31	13.56
55-59 . .	137.8	18.80	13.64	84.0	11.40	13.57
60-64 . .	141.8	21.11	14.89	84.5	12.36	14.63
Females						
16. . .	116.1	12.10	10.42	72.3	9.55	13.21
17. . .	116.0	11.51	9.92	72.0	9.16	12.72
18. . .	116.3	11.42	9.82	71.8	8.60	11.98
19. . .	115.1	11.87	10.31	71.1	8.93	12.56
20-24 . .	115.7	11.83	10.22	71.7	9.67	13.49
25-29 . .	116.8	11.43	9.79	73.7	9.05	12.28
30-34 . .	119.8	13.97	11.66	74.9	10.78	14.39
35-39 . .	123.9	13.85	11.18	78.0	10.01	12.83
40-44 . .	127.0	17.07	13.44	79.5	10.60	13.33
45-49 . .	130.6	19.47	14.91	81.5	11.63	14.27
50-54 . .	137.3	21.29	15.51	83.5	12.36	14.80
55-59 . .	138.5	21.40	15.45	83.5	11.72	14.04
60-64 . .	144.0	22.33	15.51	85.0	12.95	15.24

clinic at Kiel between 1922 and 1925. He rejected all cases with organic disease of the cardiovascular system or kidneys and those with endocrine disturbances. The blood pressures were measured with the patients seated after at least half an hour's wait. Wetherby (1932) studied the routine blood pressure readings of all individuals admitted to the medical division of the out-patient department of the University of Minnesota Hospital from December 1926 to December 1929, rejecting only clear-cut cases of glomerulonephritis and aortic regurgitation. Both Saller's and Wetherby's series show much more substantial rises of pressure with age than had hitherto been described.

In 1943 Master, Marks and Dack collected 14,849 blood pressure readings on persons over 40 years and noted the increasing incidence of higher pressures as age rose. In 1950 Master, Dublin and Marks collected the arterial pressures of 74,000 men and women obtained from sixteen industrial plants in the U.S. "The majority of persons included were at work, but the study also included those applying for employment, whether or not they were rejected." The circumstances under which the pressures were measured were not stated. From these they obtained a sample of 15,700 evenly distributed by age, and gave the mean and standard deviations for the age groups. Their results are summarized in Table 8.1.

BLOOD PRESSURE IN A POPULATION SAMPLE

This was the situation when we began our own work in 1950. Since we were interested in unravelling the influence of environment and heredity on blood pressure, it was of the greatest importance to have figures for blood pressures taken under conditions that were, as far as possible, uniform and easily reproducible, and on a sample as representative as possible of the general population. None of the previous results served quite to satisfy both of these requirements. While University entrants are a highly selected class, so far as is known the factors determining selection are not related to arterial pressure; the chief defect of this sample is its limited age range. Since high blood pressure is alleged to be a common condition, medical clinics, to which such patients would be sent, might contain an undue proportion of subjects with high pressures. Finally, although Master, Dublin and Marks' figures are impressive, the conditions under which arterial pressure was measured were not stated; nor can one be sure that, in the older age groups, subjects were not prevented from working or applying for work because of the heights of their arterial pressures.

For these reasons and because of the possibility that other local factors might influence arterial pressure, we decided to investigate the question again (Hamilton, Pickering, Roberts and Sowry, 1954a).

As we have seen in Chapter 3, a most important consideration is the conditions under which the arterial pressure is measured. So-called basal pressures have the advantage that the influence of environmental factors is minimized, but the disadvantage that such demands are made on the subject's time, that the same kind of sampling errors are introduced as by calling for volunteers. Casual pressures taken with the co-operation of the subject and after a moderate period of rest, have the advantage that these are the conditions under which the doctor ordinarily measures his patients' blood pressure. After much debate we decided that the most satisfactory population sample would be all out-patients attending during a given period at clinics for diseases not

TABLE 8.2. *Sources of population sample. (Numbers of subjects) (Hamilton, Pickering, Roberts and Soury, 1954a).*

	Group I	Group II	Group III				Total
	Varicose vein	Skins	Orthopaedic	Fracture	Dental	Total	
Female	421	513	89	143	38	270	1,204
Male	276	355	60	110	26	196	827
TOTAL	697	868	149	253	64	466	2,031

TABLE 8.3. *Population sample. Arterial Pressures (mm. Hg) by age (Hamilton, Pickering, Roberts and Soury, 1954a).*

Age	Females					Males				
	No.	Systolic		Diastolic		No.	Systolic		Diastolic	
		Mean	Standard deviation	Mean	Standard deviation		Mean	Standard deviation	Mean	Standard deviation
10-14	16	111.1	15.5	65.0	8.7	12	105.0	14.2	61.3	10.0
15-19	58	117.3	10.6	70.8	8.3	34	117.2	9.9	68.2	8.9
20-24	68	118.7	12.7	72.1	7.1	60	123.0	12.7	73.8	9.5
25-29	103	122.7	12.6	76.1	9.1	82	124.1	14.0	74.1	9.9
30-34	108	120.5	14.8	74.5	8.9	90	122.8	13.9	73.9	9.7
35-39	119	127.5	16.9	79.3	11.5	90	125.2	14.1	77.8	8.9
40-44	122	133.9	19.7	82.1	12.4	99	127.4	17.7	77.0	12.9
45-49	114	133.8	22.9	82.1	11.6	79	130.9	18.3	80.0	10.5
50-54	131	140.6	27.5	87.8	14.7	87	134.5	19.8	82.2	11.6
55-59	108	153.5	28.7	88.6	14.8	60	145.5	24.4	87.2	13.7
60-64	87	159.1	27.4	92.4	15.4	52	151.2	33.1	87.9	18.7
65-69	74	172.9	26.7	94.0	16.3	46	152.1	25.9	85.2	15.1
70-74	60	175.3	27.6	93.1	14.5	27	161.4	34.3	86.9	18.0
75-79	26	177.1	32.6	97.3	18.1	4	150.0	37.7	82.5	20.2
80-84	11	198.0	31.1	96.8	18.5	5	174.5	22.8	91.0	9.0

known to be associated with disturbances of blood pressure. Clinics for skin disease, for varicose veins, for orthopaedics, fractures and dental treatment were so chosen. Blood pressures were measured by auscultation in the out-patient hall after the subject had been seated

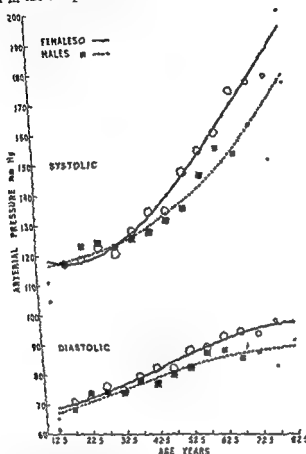


FIG 8.1 Systolic and diastolic pressures for females (open circles) and males (black squares) for each five-year age group, together with the fitted curves proportional to the number of others (1954), *Clin. Sci.*, 1.

quietly with one arm bared for ten or fifteen minutes; abrupt fading of the sounds was taken as index of diastolic pressure. Table 8.2 shows the size and composition of the sample, and Table 8.3 the mean blood pressures for each five-year age group. Both pressures rise with age in both sexes, but there are important differences between them. In order to obtain the best possible norms for arterial pressure at the different ages, curves were fitted and are shown in Fig. 8.1. In each

* The equation for male systolic pressure in our original paper has one important typographical error. The equation should read $y = 115.26 + 0.034048x + 0.0035098x^2 + 0.000057291x^3$.

sex the relationship of diastolic pressure to age was found to be adequately expressed by a straight line; but the curves shown in Fig. 8.1 are cubics, not because they give any significant improvement but because they reflect the slight flattening at older ages which is apparent in other series also. For systolic pressure, the quadratic function also gives an excellent fit in women, but not in men; although cubics give no significant improvement, they have again been used because again they lower the expected pressures at the highest ages, and it seems unreasonable to suppose that the rate of rise of blood pressure with age should continue to steepen indefinitely. Since there are comparatively few subjects in the younger and older age groups, the curves are probably less reliable at their extremes.

Comparison of Groups

The simplest way to compare data relating arterial pressure to age is to fit the best possible straight lines and see whether there is any significant difference in the position of the centres of these lines or in their slopes. This proceeding is valid for diastolic pressure since the data are adequately expressed by a straight line, but for systolic pressure it is only valid if the shapes of the curves and age distributions are similar in the series to be compared. When the sexes are so compared, the rate of increase of pressure with age, and the mean pressure as at age 45 are greater in women than in men for both systolic and diastolic pressures, the differences being highly significant. Thus in any comparison, the sexes have to be treated separately.

In selecting our population sample, we assumed that in none of the clinics were there factors operating which would render the arterial pressures different from those in the general population. To test this assumption we divided our sample into three groups: the varicose vein clinic, the skin clinic and a composite group containing the other smaller clinics. These three groups were then compared using linear regression. The regression line expresses the rate of change of one variable on another, making the simplest assumption that the relationship is of the type $y = a + bx$ where y and x are the two variables and a and b constants. This relationship as seen above is true for age and diastolic, but not systolic, pressure. Nevertheless, since age distribution is similar in the two sexes and the shapes of the curves are not very different, no serious error is introduced. The rate of rise of systolic pressure with age in females suffering from varicose veins was highly significantly greater than in the other two groups. No other difference achieved the 1 in 20 level of significance. The 1 in 20 level of significance means that such a result would occur by chance once in twenty times. Although, therefore, our population sample was not perfect, it is probably not very far from being representative of the general

population. This is reinforced by a comparison of the results of other workers, such differences as there are being attributable to differences in selection.

Effect of a Second Measurement

To obtain some idea of variability, the blood pressure was measured for a second time in 180 subjects, three weeks to four months later. The differences between the two measurements increased with age and with the height of the first reading. The direction of change was not constant, 87 showing a fall and 60 a rise on the second occasion, but for the whole series the mean change was not large, being a fall of 3.9 mm. Hg systolic and 3.6 mm Hg diastolic pressure.

Effect of Arm Circumference

As mentioned on p. 20, Ragan and Bordley (1941) showed that error in measurement by the auscultatory method using a 13 mm. arm cuff, was related to arm circumference; from this data we worked out a table of corrections (p. 22). It seemed possible that part or the whole of the relationship we had observed between arterial pressure and age was due to increasing obesity, with a consequent increasing error in measurement due to increasing arm girth. In our first sample, we did not measure arm size. It was therefore necessary to take a second sample in the same way as the first, but a year later. This second sample showed a significantly lower rate of rise of pressure with age, which was not due to the composition of the sample but was, we think, due to some of the patients having been included in the first and therefore showing the tendency to lower pressures on second measurement noted in the preceding paragraph. During adult life, arm circumference showed no appreciable tendency to rise in males, but showed a significant rise with age in females. The rate of rise of pressure, both systolic and diastolic, with age was thus not altered by correcting for arm circumference in males though it was reduced slightly in females. It may be concluded, therefore, that the rise of blood pressure with age is a real phenomenon, and not due to errors introduced by increasing arm circumference. A part, but not all of the difference between the sexes is due to this factor (Pickering, Roberts and Sowry, 1951).

The Difference Between the Sexes

The increasing disparity over the age of 40 raises the question as to whether child-bearing can have influenced pressures in the female. Barnes and Browne (1945) measured the arterial pressure in 915 nulliparous and 1,041 parous women attending out-patients for con-

ditions other than pregnancy or hypertension. They found the distribution of different arterial pressures to be the same in the nulliparous and parous women for each decade from 10 to 50 years and concluded that pregnancy neither aggravates nor causes a tendency to chronic hypertension. We subjected Barnes and Browne's data to statistical comparison in the way that we compared the two sexes of our series. Neither the pressure as at standard age near the mean, nor the rates of rise of pressure with age differ significantly in their two groups. This analysis only included women up to the age of 50; after this no age distribution is given in their data, and it is possible that an increased incidence of higher pressures in parous than in nulliparous women, which they noted, was due to inequalities in age distribution.

Arterial Pressure in Childhood

To estimate the arterial pressure in childhood, cuffs of smaller size must be used, since the 13 cm. cuff gives too low readings. In small children the diastolic pressure is difficult to measure, and Stocks (1924) found that it was often unobtainable under seven years. Although in very small children the real pressure may differ considerably from that routinely measured by the indirect method, it seems that arterial pressure rises more or less continuously from birth. Stocks measured the arterial pressure in 1,323 boys chiefly attending London elementary and secondary schools, 42 factory workers, and 154 male and 114 female students at University College, London. The measurements on schoolboys were made as part of a routine medical inspection, on factory workers as they came from work and on students at the Anthropometric Laboratory. Stocks concluded that in the male, systolic pressure rose with age, steeply from five to 17, slightly from 17 to 19 and from then remained stationary to age 39; the diastolic pressure rose continuously in childhood, the rise becoming less rapid during the first part of adolescence, followed by a rapid rise to the adult level about the end of adolescence and then gradually falling from 24 to 37 years; the pulse pressure rose continuously, but the curve showed a striking hump during adolescence from 14 to 21 years of age. In those age groups in which we have comparable figures, Stocks' values for males are much higher than ours. On the other hand, his figures for females are very similar to ours, although his numbers, particularly in the higher age groups, are small. We are inclined to attribute the differences between the figures for males to the differences in the conditions of measurement, a "routine medical inspection" and "manual workers straight from work" denoting less basal conditions than in our subjects. Nevertheless, Stocks' figures and those of Alvarez both show relatively high pressures for adolescent

TABLE 8.4. Mean Arterial Pressures observed in Childhood and Early Adult Life by Stocks (Hamilton, Pickering, Roberts and Soury, 1954a).

	Central age	No of subjects	Arterial pressure, mm. Hg	
	years		Systolic	Diastolic
Female	10	10	119.9	86.7
	21	20	121.1	79.5
	23	8	124.0	80.0
	25-29	12	122.2	77.6
	30-35	8	122.0	83.0
Male	5	36	85.27	
	7	33	91.50	67.90
	9	69	98.34	62.23
	11	75	105.79	65.15
	13	135	111.03	69.80
	15	110	123.64	74.32
	17	76	129.03	76.66
	19	21	130.36	84.17
	21	17	130.79	84.52
	22-24	40	130.10	
	25-29	24	132.00	83.83
	30-34	15	131.50	80.36
	35-39	8	128.50	76.50

The numbers for males refer to systolic pressure only: the numbers for diastolic pressure are lower in most age groups, owing to the difficulty of estimating diastolic pressures in children.

males as contrasted with females which neither Boynton and Todd nor we observed. It is difficult to know what explanation to attach to this. Some of Stocks' figures are given in Table 8.4.

Frequency Distribution at Different Ages

The frequency distribution of systolic and diastolic pressures in females and males of the population sample, arranged in five-year age groups is shown in Figs 8.2 and 8.3. It will be noted that as age advances, higher pressures tend to occur for the first time or with increasing frequency in both sexes. By contrast, low values tend to persist, though with decreasing frequency specially in women; the lowest values eventually disappear. Thus the modal pressures tend to rise in succeeding decades, and the curves tend to become broader,

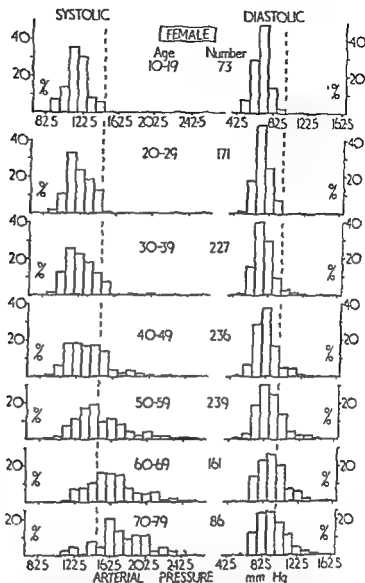


FIG. 8.2 Frequency distribution of systolic and diastolic blood pressure for females of the population sample arranged by age in decades. The histogram shows the percentages having a given range of pressure. Since the range of pressures 80-90 there were only two sets of readings, at 80 and 90.

practice of distinguishing between normal pressure and hypertension, the latter including systolic pressures of 160 mm. Hg or over and diastolic pressures of 100 mm. Hg or over. It will be seen that there is no natural division at this or any other line (Hamilton and others (1954), *Clin. Sci.*, 13, 11).

their extension to higher pressures being more conspicuous than their recession from lower values. We have already seen that arterial pressure tends to rise with age; Figs. 8.2 and 8.3 imply that the rate of rise is greater in some subjects than in others. How much greater

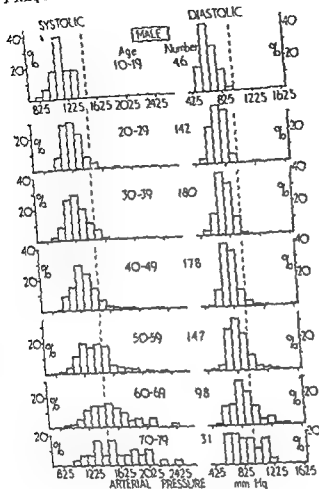


FIG 8.3 As Fig 8.2, but for males (Hamilton and others (1934), *Clin Sci*, 13, 11).

cannot be made out from curves of this kind - the distribution of individuals in this respect will be obtained about the arterial pressure over a lifetime

The frequencies of measured blood pressures depart seriously from the normal or Gaussian form of a distribution curve. One departure is positive skewness, that is to say, there are more values, and a wider range of values above the mode than below it. This, perhaps, is not unexpected, since it is known that a given stimulus seems to produce a greater change in pressure when this is initially high than when it is initially low. Pickering, Kissin and Rothschild

(1936) showed that the fall of arterial pressure produced by intravenous injection of 0.1 mg. histamine acid phosphate into subjects with high and low pressures was proportional to the initial pressure. Müller (1921) showed that the difference between the lowest day and the lowest night reading was greater in subjects with high than in those with normal pressures and was proportional to the height of the pressure. Robinson and Brucer (1939) observed that "the average range of differences between the highest and lowest readings over a ten year span varies proportionately with the level of the systolic pressure." Finally, we found that in our population sample the differences between a first and second reading were greater in those with high than in those with lower pressures (see p. 161). Thus the asymmetry of the frequency distribution curves may be attributed, at least in part, to the linear scale. Gaddum (1948) found that Alvarez' figures gave a normal curve with blood pressure plotted on a logarithmic scale.

Menopausal Hypertension

Menopausal hypertension is a condition which has been supposed to occur in women at or after the menopause, to be associated with a labile hypertension, and with a relatively good prognosis. There is no suggestion whatsoever from our figures of any discontinuity in the curves of rate of rise of pressure with age, at or about the time of the menopause, i.e. between 45 and 55 years. Taylor, Corcoran and Page (1947) undertook the care of 200 menopausal women between the ages of 20 and 59 years, 179 having been castrated. They found arterial hypertension no commoner in them than in the general population. The characteristic "hot flushes" of the menopause were not necessarily associated with hypertension; nor did their alleviation by oestrogens affect arterial pressure. Despite severe neurotic symptoms, hypertension did not develop within three or more years, except in six of these subjects.

This is in line with my own general experience. Menopausal hypertension would seem to have been an entity fabricated by imaginative minds out of the psychoneurotic and vascular events of the menopause, and the tendency for the arterial pressure of women of that age to surpass the limit arbitrarily selected as the upper limit of normal.

AGE AND SEX-ADJUSTED SCORES FOR ARTERIAL PRESSURE

One of the objects we had in mind in obtaining figures for the distribution of arterial pressures in the population at large was to use them as a yardstick against which to assess the contribution made to high blood pressure by inherited and environmental factors. A major

difficulty in carrying this out is the difference not only in means, but in the degree of scatter about these means, that is found in the two sexes at different ages. My colleague, Dr. Fraser Roberts, had met a similar problem in connection with intelligence tests and to overcome it had devised an age and sex-adjusted score (Roberts, Norman and Griffiths, 1935; Roberts and Mellone, 1952). A rather similar method had been used to compare anthropometric data obtained on twins and other siblings aged 3-15 by Stocks (1930). As we shall show in the next chapter, the distribution curves for diastolic pressure for the first degree relations of subjects with "essential hypertension" are very similar in shape to those found in the population at large, though they tend to have higher means and higher ranges. So far as the genetic aspects are concerned, there seemed a *prima facie* case for devising and using an age and sex-adjusted score, so that we could work in terms of arterial pressure, rather than in terms of normality and hypertension, an arbitrary division of data which by no means fully expresses them. Although this age and sex-adjusted score will be most extensively used in succeeding chapters, we must use it also in this and therefore proceed at once to the principles of the method and the test of its validity (Hamilton, Pickering, Roberts and Sowry, 1954b).

We begin, of course, with an actual estimation of arterial pressure. It must be stressed that this should have been obtained under circumstances as far as possible similar to those under which our population sample was investigated. The first step is to calculate the deviation of the observed value from the mean for that age and sex. The means used are given in Appendix I and were obtained from the fitted curves for our population sample shown in Fig. 8.1. As the blood pressures in the population sample were measured only to the nearest 5 mm. we also work here in units of 5 mm. The deviation of the actual value from the norm will have a + sign if it is greater and a - sign if it is lower. The frequency distribution curves shown in Figs 8.2 and 8.3 indicate that a deviation of, say, 20 mm. from the norm at age 20 is of much greater significance than the same deviation at, say, age 60. The accepted measure of variability is the standard deviation. To adjust for variability, the deviation from the norm is multiplied by the ratio of the standard deviation of the arterial pressure at some fixed age to the standard deviation at the observed age. To obtain the best figures for standard deviation over the age range studied, curves were fitted for the variance of arterial pressure on age, again using the data of our population sample; from these curves the standard deviation at any age can be read off. For systolic and diastolic pressures in both sexes, the curves fitted were cubics. Fortunately the curves for the two sexes crossed at age 23 and at age 60. At these

ages, the proportion of individuals differing from expectation by given amounts is the same in the two sexes. By choosing either as the fixed standard age to which adjustment is to be made, the sex difference is thus automatically eliminated in the age-adjusted scores. Twenty-five years would have been inconvenient because of the decision to work units of 5 mm. Hg throughout, for the steps would then have been too large. Accordingly 60 was chosen as the standard age. The division of the standard deviation as at age 60 by the standard deviation at the successive five-year age groups gives a series of multipliers. All that is necessary in order to adjust the deviation from the norm to the corresponding deviation as at age 60 is to multiply by the appropriate multiplier. To simplify this process a series of tables have been constructed and these are given in Appendix I.

The use of these scores may be illustrated by two examples, an observed systolic pressure of 135 mm. Hg in a woman of 23, and the same pressure in a woman of 60. At age 23 the expected norm is 120, and the deviation +15 mm. The multiplier is 2.453, which multiplied by 15 gives (to the nearest 5) a final score of +35 mm. Hg. At age 60 the expected norm is 155, and the deviation -20. The multiplier is, of course, 1 and the final score thus -20.

Test of the Method

To test the method scores were calculated for patients attending the skin clinic, the largest of the subdivisions of our population sample. Comparing the sexes first the result was as follows:

		Mean Score	
	No.	Systolic	Diastolic
Females	512	- 0.225	- 0.224
Males	355	+ 0.211	- 0.014
Differences		<u>0.436 ± 1.998</u>	<u>0.210 ± 1.058</u>

and
olic
nm.
- 50
six
10 mm. groups of score, the end groups comprising scores of - 20 and less and + 25 and more. The results were as follows:

	Degrees of Freedom	χ^2	P
Systolic	36	61.17	0.008
Diastolic	20	33.22	0.032

It will be seen, therefore, that the previous association between age and arterial pressure, which of course was very large indeed, has been reduced to very small limits. With the diastolic scores the association is significant though not highly so; with the systolic scores it has been reduced almost to the 1 per cent. level.

Meaning of the Age-adjusted Score

The age-adjusted score represents the number of millimetres Hg, in units of 5 mm. Hg, by which an observed pressure exceeds or falls short of the mean for the general population for that age and sex, the scores being further adjusted to what that deviation would correspond to as at age 60. In the conventional language of the contemporary clinic, these scores might thus be regarded as expressing the grade of "hypotension" or "hypertension." It is therefore of some interest to take three arterial blood pressures and calculate the

TABLE 8.5 *Age-adjusted Scores Calculated for Three Arterial Pressures at Age 20 and Age 60 in Females.*

Observed Blood Pressure		Age-adjusted scores (female)			
		Age 20		Age 60	
S.	D.	S.	D.	S.	D.
120	80	+ 10	+ 20	- 35	- 10
150	100	+ 85	+ 53	- 5	+ 10
250	150	+ 330	+ 150	+ 93	+ 60

scores for age 20 and age 60 in females (Table 8.5). The first two arterial pressures represent two of the proposed divisions between normal and abnormal. The first, 120/80, the proposed division of Robinson and Brucer (1939), yields small plus scores at age 20, and moderate minus scores at age 60. The second, one of the commonest divisions, 150/100, yields considerable plus scores at age 20, and small scores at age 60. These emphasize how absurd it is to omit age when attempting to define normality. The last pressure, 250/150, is a grossly raised arterial pressure such as is often found in patients in the malignant phase. At age 20, this gives enormous scores of +330 and +150. These are the deviations from the normal that that individual would have shown at age 60, had she survived to that age, and had arterial pressure changed with age in the ordinary way. If then we add these scores to the norms for age 60, we obtain expected pressures of 485 mm Hg systolic and 240 mm Hg diastolic. These figures are, of course, absurdly high; no figures approaching them have ever been recorded in living human beings. Are the scores, then, devoid of any meaning? On the contrary, it appears more probable that a pressure of 250/150 at age 20 is incompatible with survival to age 60, unless the arterial pressure is lowered to normal by

shall see, it is at about the blood pressure level, attained by this patient at age 20, that the malignant phase supervenes; it is probably the supervention of the acute arteriolar necroses of the malignant phase that puts a "ceiling" on arterial pressure.

One further comment is apposite to these very high pressures in young people, yielding these huge scores. Many of these patients show a discrete cause for the raised pressure, such as chronic nephritis and pycelonephritis. The age-corrected scores probably take account of these factors which operate in greater or lesser degree through the population at large. They do not take account of the less common sporadic and very potent factors, such as chronic renal disease.

Calculation of an Upper Level of Arterial Pressure Compatible with Survival to Age 60

The ideas developed in the last paragraph tempt me to one final exercise with these age adjusted scores. If one assumes, as is reasonably probable on factual grounds, that the arterial pressure taken under the conditions here

... of these calculated values as above cannot survive to age 60.

variable. To give an example from my own experience: a woman aged 43 and on many occasions, when she was used as an experimental subject, an arterial pressure of around 150/100. At ages 38 and 42, in her third and fourth pregnancies, otherwise uneventful, her arterial pressure rose to 180/120. Aged 52, her arterial pressure was 160/90. In this case, rate of rise of pressure with age differs so much from what is inferred to be the norm that a prognosis at age 23 would have proved quite misleading.

THE PROBLEM OF DEFINING NORMAL AND HIGH PRESSURES: ESSENTIAL HYPERTENSION

As has been noted in Chapter 6, and will be more fully considered in Chapters 11 and 12, the higher pressures are accompanied by certain anatomical and functional changes in the organs of the body, which, in the absence of another disease to which the high pressure can be attributed, give rise to the clinical syndrome of essential hypertension. Since the central feature of this syndrome is the arterial pressure, it is clearly desirable to define what constitutes a pathologically high pressure. Before doing so, it is necessary briefly to consider the meaning, scope and implication of the terms physiological and pathological, normal and abnormal, health and disease. Throughout the ages, the more thoughtful and spiritual of mankind have pursued good, to define them. In the same way, omena into good and bad in so far as future life expectation of mankind,

It is our constant endeavour to convert the pathological to the physiological, the abnormal to the normal, to restore the diseased to health ; in short, to make bad into good. Now all these terms are extremely difficult to define, because they are relative. Most phenomena, in fact, represent a continuous series. In a general way it is easy to regard the phenomena at one end with approval and at the other with disapproval, and to say that one is good and the other bad. But in the middle the differentiation is much more difficult ; a thing is neither particularly good nor particularly bad. These opposing concepts seem to be essential to the life of man and they permeate every aspect of his institutions and mode of thought. In the advancement of medicine in the training of the doctor it has been convenient to use them, and to distinguish between Physiology and Pathology, Anatomy and Morbid Anatomy. But this practice has led to a very artificial subdivision of knowledge and the manufacture of distinctions where none exist in Nature.

What has been just said is so commonplace as to be platitudinous. Nevertheless, it must be clearly stated, because medicine is so obsessed with the desirability of classifying phenomena under these terms, that the facts themselves are often distorted in the process, and the concept that emerges is due rather to the implications of the terms employed than to the facts on which the concept should be based. Such has happened in the case of essential hypertension. The curves of continuous variation of arterial pressure have been divided at arbitrary points into normal and abnormal, physiological and pathological, healthy and diseased, and from this division stems the concept of essential hypertension as a specific morbid entity.

If we approach the problem of the relationship between normal and pathologically high pressures with an open mind, it is clear that, broadly speaking, there are three possibilities.

(1) That normal and high pressures may differ qualitatively so that there is a sharp division between them. The difference here envisaged is one of the same order as that between round and wrinkled peas or blue and brown eyes.

(2) That normal and high pressures are qualitatively different, but overlap to a considerable extent.

(3) That there is no qualitative difference between normal and high pressures. Blood pressure is a graded characteristic like height and the differences between normal and high pressures are only of degree.

In discussing these possibilities we have assumed that we are dealing with those high pressures that are unassociated with a clearly defined causal disease, that is primary or essential hypertension. If we are dealing with secondary hypertension, the situation is quite different.

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casual pressures of these calculated values or above cannot survive to age 60.

nancies, otherwise uneventful, her arterial pressure rose to 180/120. Age-adjusted her arterial pressure was 160/90. In this case, rate of rise of pressure with age differs so much from what is inferred to be the norm that a prognosis at age 23 would have proved quite misleading.

THE PROBLEM OF DEFINING NORMAL AND HIGH PRESSURES: ESSENTIAL HYPERTENSION

As has been noted in Chapter 6, and will be more fully considered in Chapters 11 and 12, the higher pressures are accompanied by certain anatomical and functional changes in the organs of the body, which, in the absence of another disease to which the high pressure can be attributed, give rise to the clinical syndrome of essential hypertension. Since the central feature of this syndrome is the arterial pressure, it is clearly desirable to define what constitutes a pathologically high pressure. Before doing so, it is necessary briefly to consider the meaning, scope and implication of the terms physiological and pathological, normal and abnormal, health and disease. Throughout the ages, the more thoughtful and spiritual of mankind have pursued good, truth and beauty, and have sought to define them. In the same way, we in medicine seek to divide phenomena into good and bad in so far as they affect the well-being and future life expectation of mankind.

sample. Master and his colleagues use their curves to illustrate the distributions of pressures which they regard, on statistical grounds, as normal and pathological and have not commented on their form which in a general way is very similar to ours, shown in Figs. 8.2 and 8.3. All these curves tend to show positive skewness as Alvarez (1920) found. A more complete analysis has been made on the curves obtained after applying the adjustments for age and sex described on p.166. Fig. 8.4 shows three such curves: (a) for a section of our

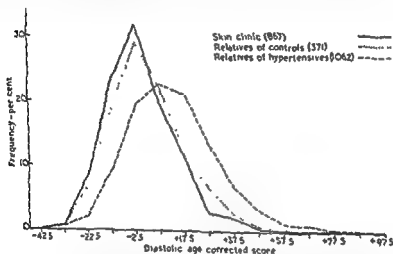


FIG. 8.4 Frequency distribution of age and sex-adjusted scores for diastolic pressure for three samples (Hamilton and others (1954), *Clin. Sci.*, 13, 37).

Tests for Normality of Curves. Using third and fourth moments for testing for normality it was found:

	μ_3	μ_4
For (a)	$+1.122 \pm 0.0830$	$+3.837 \pm 0.1684$
" (b)	$+0.832 \pm 0.1287$	$+1.483 \pm 0.2543$
" (c)	$+0.610 \pm 0.0751$	$+0.760 \pm 0.1503$

All these curves thus show pronounced positive skewness, but there is also the evidence of positive kurtosis, too many observations in the upper tail.

A consideration of the shape of the distribution curves thus leaves unanswered the question as to whether one, or more than one, population is involved.

arterial pressure as one of its striking features. In secondary hypertension there is a strong case for believing that we are dealing with a process that may be qualitatively different from normal, though except in the paroxysms of phaeochromocytoma the precise nature of this is unknown. Secondary hypertension is, however, relatively rare,¹ and so far as the population at large is concerned, it is unlikely that it occurs frequently enough seriously to affect the issue under discussion.

It is obviously a very convenient assumption that normal and pathological pressures are sharply divisible, and most writers and workers in practice accept this solution, and, by implication, the first possibility listed. The suggestions that have been made as to the place of this division have, however, varied from 120/80 (Robinson and Brucer, 1939) to 180/110 (Evans, 1948). Many workers admit there is no sharp division, but, even so, regard hypertension as qualitatively different from normal and appear to accept the second possibility. Our investigations have led us provisionally to accept the third as the most likely possibility. The evidence on which this question may be decided is as follows:

(1) Do the Distribution Curves Indicate One or Two Populations?

Frequency distribution curves for blood pressure at various ages have been produced amongst others by Alvarez (1920), Master, Garfield and Walters (1952) and ourselves. When pressures are grouped in units of 5 mm., the curves tend to show peaks at the 10s, a feature almost certainly due to the preference of doctors to read to the nearest 10 rather than $\frac{1}{2}$ mm. Allowing for this, Alvarez (1920) made a careful analysis of the shape of his curves and noted that the normal form² was followed fairly closely except at the ends, there being too many rather low and too many rather high values. Thus he calculated from the general shape of his curves that only one man in 10,000 should have a systolic pressure over 175 mm. Hg, but there were, in fact, eight in 2,930 in his series, a proportion of 27 to 10,000. This excess he attributed to hypertension. It is, of course, quite possible, though equally unproven, that this excess of 26 per 10,000 represented the incidence of secondary hypertension of this degree in his population.

¹ It is a curious lapse that there are no figures known to the author to show just how common the different forms of hypertension are in a population sample. There are, of course, figures (see Platt, 1947) for the proportion of renal lesions in apparently essential hypertension, but nearly all these series are selected and thus may provide misleading figures.

² "The shape of normal curves will be found

(2) *The Statistical Approach*

The probability that any pressure is abnormal is, to quote Master, Dublin and Marks (1950), a statistical question and as such admits a statistical answer. "The usual yardstick is the standard deviation, σ . In a normal distribution, roughly two-thirds of the observations will be found within the range of the mean $\pm \sigma$ and approximately 95 per cent of the observations will be within the range of the mean

TABLE 8.6. *Normal Range and Limits of Hypotension and Hypertension (Master, Dublin and Marks, 1950).*

Sex, Age	Systolic *			Diastolic *		
	Hypo- tension Upper Limit	Normal Range	Hypertension Lower Limit	Hypo- tension Upper Limit	Normal Range	Hypertension Lower Limit
Males						
16	98	105-135	145	52	60-88	90
17	98	105-135	145	55	60-88	90
18	98	105-135	145	53	60-88	90
19	98	105-140	150	53	60-88	95
20-24	98	105-140	150	56	62-88	95
25-29	100	108-140	150	60	65-90	96
30-34	100	110-145	155	60	68-92	98
35-39	102	110-145	160	60	68-92	100
40-44	102	110-150	165	60	70-94	100
45-49	104	110-155	170	60	70-96	104
50-54	105	115-160	175	60	70-98	108
55-59	106	115-165	180	60	70-98	108
60-64	108	115-170	190	60	70-100	110
Females						
16	95	100-130	140	55	60-85	90
17	95	100-130	140	55	60-85	90
18	95	100-130	140	55	60-85	90
19	95	100-130	140	55	60-85	90
20-24	95	100-130	140	55	60-85	90
25-29	98	102-130	140	55	60-85	90
30-34	98	102-135	145	55	60-88	95
35-39	100	105-140	150	60	65-90	98
40-44	100	105-150	165	60	65-92	100
45-49	100	105-155	175	60	65-96	105
50-54	105	110-165	180	60	70-100	108
55-59	105	110-170	185	60	70-100	108
60-64	105	115-175	190	60	70-100	110

* Blood pressure readings in millimeters of mercury

tion is concerned as regards arterial pressure. What is abundantly clear is that there is no sharp division into normal and abnormal. This is well illustrated by the distribution curves shown in Figs. 8.2 and 8.3 in which dotted lines have been drawn at one of the commoner contemporary divisions, 150 mm. Hg systolic and 100 mm. Hg diastolic. That these or any other dividing lines are completely arbitrary

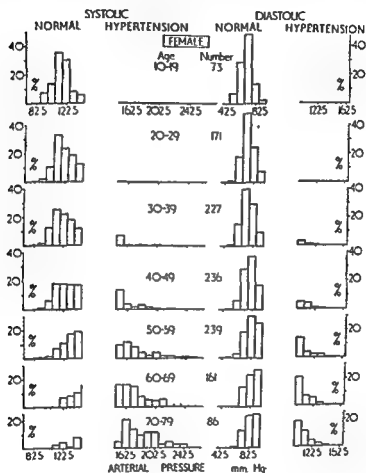


FIG. 8.5. The continuity of the division is clearly revealed.

rary, and not based on the characteristics of the curves is evident from the figures without further discussion. What happens if the conventional practice is followed of dividing the population into "normal" arterial pressure and "pathologically high" arterial pressure is shown clearly in Fig. 8.5. Here the distribution curves for blood pressure in females in the population have been actually separated at the arbitrary point of division. The "normal" curve ends, the "abnormal" begins, in a precipice.

(2) *The Statistical Approach*

The probability that any pressure is abnormal is, to quote Master, Dublin and Marks (1950), a statistical question and as such admits a statistical answer. "The usual yardstick is the standard deviation, σ . In a normal distribution, roughly two-thirds of the observations will be found within the range of the mean $\pm \sigma$ and approximately 95 per cent of the observations will be within the range of the mean

TABLE 8.6. *Normal Range and Limits of Hypotension and Hypertension (Master, Dublin and Marks, 1950).*

Sex, Age	Systolic *			Diastolic *		
	Hypo- tension Upper Limit	Normal Range	Hypo- tension Lower Limit	Hypo- tension Upper Limit	Normal Range	Hypo- tension Lower Limit
Males						
16	98	105-135	145	52	60-86	90
17	98	105-135	145	55	60-86	90
18	98	105-135	145	65	60-86	90
19	98	105-140	150	65	60-88	95
20-24	98	105-140	150	66	62-88	95
25-29	100	108-140	160	60	65-90	90
30-34	100	110-145	165	60	68-92	98
35-39	102	110-145	160	60	68-92	100
40-44	102	110-150	165	60	70-94	100
45-49	104	110-155	170	60	70-96	104
50-54	105	115-160	175	60	70-98	106
55-59	106	115-165	180	60	70-98	108
60-64	108	115-170	190	60	70-100	110
Females						
16	95	100-130	140	55	60-85	90
17	95	100-130	140	55	60-85	90
18	95	100-130	140	55	60-85	90
19	95	100-130	140	55	60-85	90
20-24	95	100-130	140	55	60-85	90
25-29	98	102-130	140	55	60-85	90
30-34	98	102-135	145	55	60-86	92
35-39	100	105-140	160	55	60-88	95
40-44	100	105-150	165	60	65-90	98
45-49	100	105-155	175	60	65-92	100
50-54	105	110-165	180	60	65-96	105
55-59	105	110-170	185	60	70-100	108
60-64	105	115-175	190	60	70-100	108

* Blood pressure readings in millimeters of mercury.

$\pm 2\sigma$. Obviously, since there is no sharp dividing line between clearly normal and clearly abnormal levels of blood pressure, the limits of normal blood pressure, even by a statistical definition, must be arbitrary. Certainly we may assume that any reading within one standard deviation of the mean is probably within the normal range, and it is not unreasonable to extend this normal range to cover 80 per cent of the observations, that is, 40 per cent on either side of the mean. On the other hand, any blood pressure reading departing 2σ or more from the mean is probably abnormal." The figures obtained for the normal range of arterial pressure, for the upper limits of hypotension and for the lower limits of hypertension are shown in Table 8.6. The normal range includes 40 per cent. of the observations above, and 40 per cent. of the observations below the mean, and the limits of hypotension and hypertension are -2σ and $+2\sigma$ from the mean.

Master, Garfield and Walters (1952) have recently made a strong plea for accepting these figures as new limits for normal pressure and hypertension. So long as it is clear that in this connection normal pressure represents the central 80 per cent. and the pathological pressures the extreme 5 per cent. of values found at that age in a population sample, no harm can come. But that is all that these new figures mean. They must not imply that the 5 per cent. at the extremes represent a group of individuals who differ qualitatively as regards blood pressure from the rest of the population. That, unfortunately, is the real danger of the acceptance of any definite figure as meaning "hypertension."

(3) *Does Normal Arterial Pressure Rise with Age?*

In a paper which has received a wide acceptance and has had a profound influence on thought and practice, Robinson and Brucer (1939) proposed that a *strictly normal pressure* is 120/80 or less and does not rise with age, that a systolic pressure of 120 to 130 constitutes a potential hypertension and over 130 an actual hypertension. Their conclusions are based on the records of 7,478 men and 3,405 women, a group which "while based on accepted risks for life insurance companies, represents for the most part persons examined long after the original policy examination." They found that if they excluded all subjects with pressures over 140/90 the remainder showed no significant rise of pressure with age. Of those with pressures below 140/90, 60 per cent. had pressures under 120 systolic and 80 diastolic. In a ten-year follow-up of 500 subjects, they found no significant rise of pressure in those with pressures initially below 120/80. This paper is open to very serious criticism. In the first place they deal with a selected group of insurance policy holders; they make two further selections from this group, and their final selection is followed for as short a

period as one decade. Master, Dublin and Marks (1950) pointed out that Robinson and Brucer's conclusions were incompatible with their data. That they are quite incompatible with ours is evident from Figs. 8.2 and 8.3. Thus in the age group 60-69 only 21 per cent. of the men and 10 per cent. of the women had systolic pressures below 120 mm. Hg in our series. It is, of course, possible that there may be a fraction of the population in which arterial pressure does not rise with age, but the histograms suggest that this fraction, if it exists, must be small, scarcely meriting the term "normal." It seems, in fact, from our data that there is a general tendency for arterial pressure to rise with age, but that pressure rises more in some than others. How big these differences are cannot be decided from figures of this kind, but there is evidence that will receive attention later to suggest that differences in the rate of rise of pressure with age may result from differences in environment.

By a careful review of the histories of 2,147 patients attending the clinic for hypertensive vascular disease at the Presbyterian Hospital, New York, Perera (1948) has concluded that the onset of hypertension was under the age of 40 in 92 per cent and under the age of 48 years in all. He tends to accept Robinson and Brucer's figures and states that the normal resting pressure on repeated examination by the same

observer is usually 90 mm. of mercury. It becomes increasingly probable the more often this value is exceeded." "The diagnosis of hypertensive vascular disease rests at present on the repeated finding of hypertension when other causes of diastolic blood pressure elevation can be excluded." Perera's views would seem to imply that if the casual diastolic pressure has not reached 90 mm. Hg by the ages of 40 and 50, it is respectively improbable and impossible that it should ever do so, unless other causes intervene. Perhaps the operative words are "other causes." In our population sample the percentages in the fifth, sixth and seventh decades having diastolic arterial pressures of 95 mm. Hg or over were respectively 13, 29 and 45 for women, and 9, 22 and 30 for men. There is no suggestion from our data for the view that the proportion of women and men, whose diastolic pressures have not reached 90, stays the same as age advances beyond 50 years.

(4) Arterial Pressure and Expectation of Life

The fourth argument which has been used for dividing normal arterial pressure and hypertension is that expectation of life diminishes with rise of arterial pressure. The early figures of insurance companies showed that in the young

ARTERIAL PRESSURE IN POPULATION

Classified According to Diastolic and Systolic Readings ; By Ages at Issue, Standard and Substandard Issues Combined, Experience from 1925 to 1938 (Dublin, Lotka and Spiegelman, 1949).

Systolic mm.	Diastolic (Fifth Phase), mm.													
	Ages 10-29							Ages 30-39						
	64-73	74-83	84-88	89-93	94-98	99-103	104-108	64-73	74-83	84-88	89-93	94-98	99-103	104-108
108-117	†	†	126	*	—	—	—	†	†	73	*	*	—	—
118-127	†	†	103	113	132	—	—	†	†	93	115	106	—	—
128-132	101	100	101	107	160	*	*	95	95	107	125	117	*	*
133-137	90	78	101	127	*	—	*	119	119	120	153	160	*	*
138-142	*	106	96	128	*	—	—	107	107	121	142	198	284	*
143-147	—	*	*	*	*	—	*	*	*	152	144	205	*	*
148-157	*	*	*	*	*	*	*	—	*	*	193	246	308	*
Systolic mm.	Diastolic (Fifth Phase), mm.													
	Ages 40-49							Ages 50 and Over						
	64-73	74-83	84-88	89-93	94-98	99-103	104-108	64-73	74-83	84-88	89-93	94-98	99-103	104-108
108-117	†	†	94	*	*	—	—	†	†	123	*	*	—	—
118-127	†	†	86	103	122	—	—	†	†	72	78	122	—	—
128-132	93	95	98	103	107	*	*	85	85	93	92	98	*	*
133-137	111	103	109	118	139	*	*	84	91	96	97	100	95	—
138-142	121	119	130	146	170	166	*	104	101	106	118	132	118	*
143-147	*	146	142	176	225	168	*	119	131	118	125	140	150	*
148-157	*	204	196	212	223	304	411	115	130	152	148	180	213	213
158-167	*	*	*	221	408	421	*	*	185	171	192	218	211	326

† Blood pressures within normal range (systolic readings below 128 mm. and concurrently the diastolic readings below 84 mm.) not included in this investigation.

* Less than 25 actual deaths were observed in this category.
Source : The Actuarial Society of America and The Association of Life Insurance Medical Directors of America, " Blood Pressure Study, 1939," New York, 1940.

the pressure was very low or high. These figures did much to favour the conception of low and high blood pressure as specific morbid entities meriting the serious attention of the clinician. The authoritative figures which have since been published by insurance companies cover only a limited range of arterial pressure since those with high pressures initially are not accepted as risks.

Table 8.7 is taken from the book of Dublin, Lotka and Spiegelman (1949) and shows the detailed experience of insurance companies

TABLE 8.8. *Mortality Ratios† for Men according to Groups of Systolic and Diastolic (Fifth Phase), Blood Pressure Readings, Without Minor Impairments, All Entry Ages Together (from the Actuarial Society of America and The Association of Life Insurance Medical Directors, 1941).*

Systolic reading (mm.)	Diastolic reading (5th Phase)—mm.				
	64-83 %	84-88 %	89-93 %	94-103 %	All %
118-132	90 *	91	99	97	92
133-142	99	107	118	134	110
143-152	133	137	141	173	148
153-167	186	178	189	237	210
All	95	100	116	151	106

* This included only systolic readings 128 to 132 mm.

† Actual to expected deaths (expected = 100).

concerning the influence on subsequent mortality of various systolic and diastolic pressures recorded at various ages at first examination. Comprehensive figures have been produced by the Actuarial Society of America and the Association of Life Insurance Medical Directors, 1941, and 1949.

nated

minor

pressure It will be noted that the rise is at first gradual and later steeper, as is also seen in Robinson and Brown's work. The range of arterial pressures of "normality."

n 100 mm.

Clearly,

justifying a sharp distinction between normal and abnormal.

The Actuarial Society's figures (1941) show the effects of other minor abnormalities on expectation of life. With one minor impairment the largest increases in mortality occurred when this was circulatory (+21 per cent.) or genito-urinary (+23 per cent.) and the only decrease (-4 per cent.) occurred with a family history of tuberculosis or other deaths.

Dublin, Lotka and Spiegelman's comment on their data is both authoritative and informative. They state :

"It is clear from the table that mortality rises steadily and markedly with increasing elevation of both the systolic and diastolic

TABLE 8.9. *Deaths from Cardiovascular-Renal Disease. Ratios of Actual Deaths to those Expected for this Cause in the Basic Table. All Entry Ages Together (from the Actuarial Society of America and the Association of Life Insurance Medical Directors, 1941).*

Systolic reading (mm.)	Diastolic reading (5th Phase) — mm		
	54-83 %	84-93 %	94-116 %
108-132	86	101	116
133-142	103	137	171
143-177	175	201	293

pressure. The significant increase found in mortality with relatively moderate elevation of blood pressure was contrary to clinical impressions. The classes relating to hypotensives indicate that in general such persons have a low mortality. These findings are in conformity with the clinical impressions and earlier insurance investigations of persons with low blood pressure.

"The excessive mortality among the hypertensives is primarily due to the cardiovascular-renal diseases. With increasing departure from average blood pressure, the ratios of actual to expected deaths increased faster for the cardiovascular-renal diseases than for all causes. In the group with the highest blood pressures included in this experience—and these are not considered seriously high by many clinicians—the mortality from cardiovascular-renal diseases was nearly $4\frac{1}{2}$ times the average for all standard risks "

The relationship between arterial pressure and death from cardiovascular-renal disease is so important that it may be said to be the focal point of our problem. This relationship is further illustrated by Table 8.9 which shows the steady increase of deaths from cardiovascular

disease as the arterial pressure of the accepted insurance candidate rises. Here again there is no sudden break.

General Comment

The facts here considered exclude the first possibility, namely that normal blood pressure and hypertension are clearly defined separate conditions. Either of the remaining hypotheses, namely that they are qualitatively different, but overlap, or that the difference is quantitative and not qualitative, is consistent with the facts. The genetic analysis described in the next chapter suggests that arterial pressure is a graded characteristic and thus that the difference is quantitative. There is also a more general consideration that has a similar implication.

The frequency distribution curves (Figs. 8.2 and 8.3) show that at any age most subjects have pressures near the mean, but some have values that are higher, others values that are lower, and in the older age groups the extremes are widely separated. What we call essential hypertension is obviously the right-hand end of the distribution curve and different authorities chop it off at different points. In biological

... quantitatively distinct, present in the individuals represented in that section of the curve and absent in the others. It would seem on general grounds that the arterial pressure is the resultant of a number of factors, some of which occur widely in the general population, others of unusual potency are more sporadic. In terms of current clinical notation, essential hypertension may be regarded as the resultant of several factors of widespread occurrence that affect the population at large; secondary hypertension as more particularly the resultant of single potent sporadic factors arising from the disease concerned.

Thus we may restate the definition of essential hypertension as follows: essential hypertension represents that section of the population with arterial pressures above a certain value, selected on arbitrary grounds, and in whom there is no other disease to which the high pressure can be attributed.

This conception of essential hypertension puts in perspective some of the peculiarities of its natural history to which attention has previously been drawn. Platt (1948) has pointed out that severe hypertension in young persons is nearly always

... produce a conspicuous rise of ... the probability of an inter- ... factor becomes ex

increases with age is also clear. Again the finding that a transient hypertension has years later become a permanent hypertension is a simple consequence of the variability of blood pressure, the tendency of pressure to rise with age and the definition of hypertension as a value of arterial pressure exceeding a certain level.

It may with justice be asked whether there is any point in retaining the term and the concept of essential hypertension. The really important facts that emerge are that at any age mortality is directly related to blood pressure, and that the excess of deaths in those with higher pressures are largely cardiovascular-renal. The higher levels of pressure are thus of some consequence to their owners, largely, as we have seen, owing to increased liability to vascular disease. It is convenient to have a name to describe people whose pressures are in the higher ranges, and essential hypertension is a name of long usage. What has produced so much harm is the practice of drawing a line and saying that on one side the pressure is normal and on the other abnormal. Some of the harm is a consequence of the practice of naming diseases, which tend to be regarded by the generality of doctors as just as distinct from one another as are the species of plants and animals; thus has developed the concept of essential hypertension as a specific disease entity and the long and futile search for a single specific cause. Of greater immediate importance is the obscuring of the facts concerning the epidemiology of arterial pressure discussed in this chapter.

I am convinced that any division into normal blood pressure and hypertension is quite arbitrary, and the benefits of such a division are small compared with the ill-effects. The only benefit is to ease the task of the overworked doctor, by providing him with a clear-cut answer that saves him the trouble of assessing the whole patient, the whole problem of the consequences of high pressures and the extent to which they may be prevented. So far as insurance companies are concerned, any such division is clearly useless, since expectation of life is at least in part a function of arterial pressure, and there are enough data, over the lower parts of the range at least, to allow assessment of individual readings. But the practice does real harm to the patient and to those who would try to unravel the problem of essential hypertension. One of my most impressive experiences as a physician interested in cardiovascular disease has been the immense amount of harm that is done by informing men and women, particularly young men and women, that they have high blood pressure, when there is no treatment available to alter their lot, this is an experience which I have had in visiting all continents of the globe bar one; and I have no reason to suppose that, were that omission repaired, I should have cause to revise this opinion. This is an impor-

tant question and will be further considered under treatment. While an ordinary ability to sympathize with my fellow creatures has long convinced me of what I have just stated, it is only recently, in fact since the work described in this chapter was done, that I have realized how completely my own understanding of the problem of essential hypertension—and I think in this my contemporaries are no different—has been obstructed by this practice. The realization of this has, in fact, been one of my greatest experiences as a clinical research worker. After twenty-three years of work centred on the problem of hypertension, it was as though the veil had been lifted, and I realized that the problem of the cause of essential hypertension is the problem of the cause of the variations in pressure in the population at large. The hereditary and environmental factors concerned are discussed in the next two chapters.

SUMMARY

The problems considered in this chapter have been bedevilled by the concepts normal and abnormal, healthy and unhealthy, physiological and pathological, into which categories it has long been the practice to try and force all phenomena that affect the well-being and expectation of life of man. These terms are essentially relative, and insistence on their use, may in this as in other instances obscure the facts and prejudice the issues.

Arterial pressure rises with age and more in some subjects than in others. At any age, variation is constant. . . .
 though on present evidence . . .
 tion of life diminishes . . .
 is non-linear, mortality increasing faster than arterial pressure. What is currently designated essential hypertension represents a . . .

pressure; the difference is not of kind but of degree.

CHAPTER 9

THE RÔLE OF INHERITANCE IN ESSENTIAL HYPERTENSION

HISTORICAL BACKGROUND

It has long been suspected that genetic factors were concerned in the genesis of hypertensive cardiovascular disease. Morgagni (1769) mentioned the case of Zani who died from a cerebral hæmorrhage and whose father had died from apoplexy. Since simple and reliable methods of measuring the arterial pressure were introduced at the end of the last, and have been increasingly used in this, century, evidence based on actual readings of arterial pressure has also become available.

The evidence concerning the rôle of inheritance in essential hypertension is of four kinds : records of single families, studies of family histories in large series of patients, measurements of blood pressure in twins, and measurements of blood pressure in the relatives of patients with essential hypertension.

Records of single families, such as those of Rosenbloom (1923), while suggestive, are of little value, since in a condition as common as essential hypertension, such occasional aggregations might occur by chance. Studies of family histories have yielded results that seem to depend on the care expended on obtaining them. Weitz (1923) found a history suggestive of hypertension in one or both parents in 76.8 per cent. of 82 patients with essential hypertension, and a similar history in the parents of 30.3 per cent. of 267 control patients over 44 years, attending his clinic for complaints other than cardiovascular. O'Hare, Walker and Vickers (1924) found positive family histories in 68 per cent. of 300 cases of essential hypertension, and in 37.7 per cent. of 436 control cases. Platt (1947), by personal enquiry, obtained a history which he regarded as positive for hypertension in the parents in 59 per cent. and negative in 6.4 per cent. of 78 patients with essential hypertension, as compared with 25.5 per cent. positive and 34.6 per cent. negative in 55 patients over the age of 40 without hypertension. On the other hand, Nuzum and Elliot (1931) analysing case records, and Feldt and Wenstrand (1943), analysing the records of 2,188 applicants rejected for insurance because of hypertension, and 2,188 applicants of similar age and sex, accepted by the same company during the same period, found differences in the incidence of family histories of cardiovascular disease that were so slight as to be of

doubtful significance. Two major criticisms may be made of such studies. Firstly, it is a general criticism of hearsay evidence obtained from patients, that they are more likely to have remembered details of illness of their relatives if they think that they have any bearing on their own maladies. Secondly, these histories are indicative of structural arterial disease rather than hypertension, and while the two are related, they are far from synonymous. Thus Weitz (1923) accepted death from heart failure or a stroke as indicative of hypertension. The recorded frequency of the causes of death in hypertension has varied much with the way in which the series has been selected, as may be seen from the figures collected by Fishberg (1939) and by Bechgaard (1946), Bechgaard's own figures are a fair sample: 45 per cent. died from cardiac disease, 16 per cent. from stroke, 10 per cent. from uræmia and 23 per cent. from intercurrent disease. Whilst heart disease is thus the commonest form of death in essential hypertension, it does not follow that essential hypertension is always found in elderly subjects dying with cardiac failure. In Cassidy's (1940) series of patients with coronary disease, 21.7 per cent. had blood pressures over 200/120, 33.7 per cent. had pressures between 160/100 and 200/120, and 44.6 per cent. had pressures below 160/100 mm. Hg. Thus family histories are an inaccurate guide to high blood pressure in that they may omit a considerable proportion of subjects who, in fact, had raised pressure and include a similarly considerable proportion of those who had not.

Measurements of blood pressure on monozygotic and dizygotic twins are of great importance as evidence of the extent to which arterial pressure depends on inherited factors. Stocks' (1930) investigation of arterial pressure in twins aged 3 to 15 in London schools showed a greater correlation between members of monozygotic than dizygotic pairs. Such would seem also to be the results of investigations by v. Verschuer and Zipperlen (1929), in which the mean differ-

lected, but in fact many were traced from the records of health insurance agencies and from a home for heart disease. Where both members had systolic pressures under 150 mm. Hg they found that the difference between the two members averaged 6.3 mm. Hg in 12 monozygotic pairs and 11.4 mm. Hg in 18 dizygotic pairs. When one member had essential hypertension (blood pressure over 160 mm. Hg.) the differences in systolic pressure was 26.4 mm. Hg. for seven monozygotic twins and 36.8 mm. Hg. for 12 dizygotic twins. In their own monozygotic series, when the difference between members of a pair was large, they always found that the heavier member had the higher blood pressure,

despite his life having often been less strenuous psychologically and physically. They conclude that while inheritance may be a necessary factor in the production of essential hypertension, environmental factors contribute, and of these the most important is diet. Other experience has, however, been different. In twins aged 21 (Flynn, Kennedy and Wolf, 1950), the thinner twin that had more illnesses had the higher pressure and in Friedman and Kasanin's (1943) pair it was also the lighter that had the higher pressure. Apart from these studies, the remaining cases reported are chiefly casual case reports which are summarized by Weitz (1941). One of these case reports is worth mentioning. Klemola (1938) reported identical twins whose blood pressures were raised at the age of 23, and at 27 were 185-210/105, and 170-200/105 respectively. Their father, aged 52, had a pressure of 145/95, and their mother, aged 51, a systolic pressure of 135 mm. Hg. Both parents had ancestors and siblings who might have had hypertension. Klemola concluded that in this instance hypertension was inherited as a recessive trait. Unfortunately, the possibility that the hypertension was secondary to another congenital lesion such as a renal abnormality or coarctation of the aorta does not seem to have been excluded, a criticism which can be made of many of these twin studies.

Weitz (1923) recognized the possible fallacies in family history studies and he therefore measured the blood pressure in 93 brothers and sisters of 42 patients with essential hypertension and noted that the incidence of hypertension was greater in them than in 359 control subjects of similar age (over 45 years), attending his out-patients for complaints other than cardiovascular, and for diseases other than those influencing blood pressure. In both relatives and controls he noted that the incidence of hypertension rose with age. He argued, therefore, that if an inherited factor were responsible, hypertension might display itself at different ages in different families. Confining attention to 47 relatives born earlier than the patients, he found the ratio of those with hypertension to those without was 20 : 27 if 150 mm. Hg was taken as the dividing line, and 18 : 29 if 160 were accepted. Among the relatives who were born before the patients, 11 had died of heart disease or stroke; had these survived they would probably have been examined and found to have hypertension. Thus the ratio between those with hypertension and those without approached 1 : 1¹ and suggested a dominant type of inheritance, a hypothesis which was supported by family histories of the disease extending into three generations. Weitz looked carefully into the other exogenous factors alleged to play a part in the pathogenesis of hypertension and

¹ Weitz does not mention relatives who had died from diseases other than cardiovascular, and who had they lived might have swelled the numbers of those without hypertension. But by choosing his dividing line appropriately he could still have got a 1 : 1 ratio.

found no evidence for any of them. He concluded that such factors as hard physical work, infections and psychical disturbance, played no part in determining hypertension, but might be the means of bringing a patient with hypertension to the doctor.

In 1933, Allan reported briefly a statistical investigation into the inheritance of hypertension, based partly on blood pressure measurement and partly on family histories. From published figures he estimated the frequency of hypertension (over 160/100) as 40 per cent. in the general population over the age of 60. In 485 patients with hypertension he found that 480 gave a family history of hypertension, apoplexy, congestive heart failure or sudden death in both parents in 27 per cent, and in one parent in 72 per cent. If the trait were inherited as a dominant, the expected figures would have been 34 per cent. for both parents, and 67.5 per cent. for one; if recessive, 40 per cent. for both and 46.5 per cent. for one. Making similar comparisons between the calculated and observed incidences of hypertension in siblings and offspring, he concluded that there was suggestive evidence that hypertension was inherited as a dominant, but the facts were too few to warrant a definite conclusion.

In 1934, Ayman measured the blood pressure in 1,524 members of 277 families, by collecting as many relatives as possible when they came to visit patients in the wards. He found that the incidence of hypertension (over 140/80) in offspring aged 14-39 was 3.1 per cent. if no parent had hypertension, 28.3 per cent. if one parent had hypertension, and 45.5 per cent. if both parents had hypertension. He also found that of 70 brothers and sisters of patients with hypertension, 37.3 per cent. had elevated blood pressures, whereas of 86 brothers and sisters of parents with hypertension 65.3 per cent. had elevated blood pressures (140/85 or more). He considered his figures provided evidence for a hereditary factor in hypertension.

1. Patients admitted to hospital with pregnancy toxæmia and in 66 relatives of 47 pregnant women with normal pressures. They found the incidence of hypertension in the relatives of patients with eclampsia and pre-eclampsia was much the same as in the relatives of normal women, while in the 55 relatives of 26 patients with essential hypertension the incidence of hypertension was abnormally high. They did not analyse their figures statistically, but concluded that there was a hereditary element in essential hypertension.

The most extensive measurements were those of Soby (1948) who measured the pressures in relatives of 186 patients with hypertension due to nephrosclerosis. His nephrosclerosis corresponds, though

not exactly, with malignant essential hypertension. Parents, parents' siblings, siblings and offspring were investigated, but only if over the age of 30, since, he considered, hypertension was rare below that age. Sobyé obtained details of 2,023 relatives, by his own personal examinations in 37.2 per cent., from hospital records in 17.9 per cent., from general practitioners in 8.5 per cent. and from death certificates in 36.4 per cent. He found a disposition to hypertension in one generation in 22.6 per cent., in two generations in 61.3 per cent., in three generations in 10.2 per cent. and in four generations in 0.5 per cent. of the families investigated. He measured the arterial pressure in the relative's house after a history had been obtained, with the subject sitting at rest for at least half an hour. Unfortunately, Sobyé did not have time to investigate similarly a control series of relatives of subjects with

certain surgical wards for three years, rejecting those with diseases known to be associated with high or low blood pressure. The blood pressure was taken with the patient lying down, and was repeated the following day, if it was high. For each of the relatives of hypertensive subjects, he selected from his control series consecutive cases that matched for age and sex, and compared the incidence of hypertension in the two. For each class of relative (fathers, mothers, brothers, sisters, sons and daughters) hypertension (160/100 or over) was more frequent than in the control series. Apoplexy and nephrosclerosis were much more frequent in the relatives than in the general population. From these observations, and scrutiny of individual families, Sobyé considered that both nephrosclerosis and essential hypertension were inherited through a gene behaving as a Mendelian dominant and having a frequency in the population of 30-40 per cent.

These observations taken together make it probable that inheritance plays an important rôle in the pathogenesis of essential hypertension. Nevertheless, they are inadequate to answer the very important questions of the nature of the genetic factor and its size. The data are strikingly defective in control observations on the population at large or on relatives of subjects without hypertension; moreover, all analyses begin with the highly dubious assumption that there is a sharp dividing line between normal blood pressure and hypertension. It would seem possible to make almost any data compatible with any genetic hypothesis by choosing an appropriate age group and an appropriate blood pressure and hypertension views adopted have been a consequence not so much of the data, but of the assumptions made in interpreting them.

A NEW INVESTIGATION OF THE PROBLEM

This was the position from which Sowry, Hamilton and I started our own observations in 1949. The question we actually set out to answer was "Is essential hypertension inherited as a Mendelian dominant?" It seemed clear to us that to answer this question we must depend on measurements of blood pressure, since after all, it is this value and nothing else, which is under investigation. Measurements would have to be made on the first degree relatives¹ of subjects with essential hypertension, and on a comparable sample of relatives of subjects of similar age without hypertension. It also seemed important to obtain similar measurements on a sample of the general population in order to obtain figures for gene frequency.

Choosing the Samples

We began with the concept from which all previous work had started that essential hypertension was a discrete entity. We met the usual difficulty of how to define hypertension, and we resolved it so far as the *propositi*² were concerned by accepting diastolic pressures of 100 and over as high, and pressures of 85 mm. and less as normal. Our *propositi* with hypertension thus had diastolic pressures of 100 mm. Hg or more, and were not suffering from any of the known causes of secondary hypertension; patients in the malignant phase of hypertension were also excluded. Our control *propositi* had diastolic pressures which were not known to have exceeded 85 mm. Hg. A single reading of casual arterial pressure was obtained in the relatives, when they came to visit the *propositi* in hospital, by one of us visiting them at home, or from their doctors. In this way, we obtained comparable readings in 373 of the 485 living first degree relatives of 102 *propositi* with normal blood pressure and in 376 of the 451 living first degree relatives of 109 *propositi* with essential hypertension. The analysis and interpretation of these figures was chiefly due to Dr. J. A. Fraser Roberts, who joined us later.

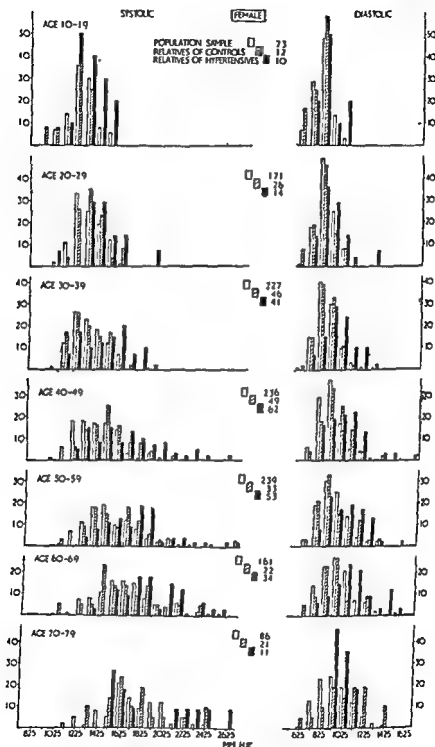
The Basic Data and their Analysis

The results obtained on the population sample have been described in the previous chapter. Figs. 9.1 and 9.2 show the distributions of pressures in the population sample and in the two series of relatives and Figs. 9.3 and 9.4 show the linear regression lines³ of blood pressure on age for the population sample and the two series of

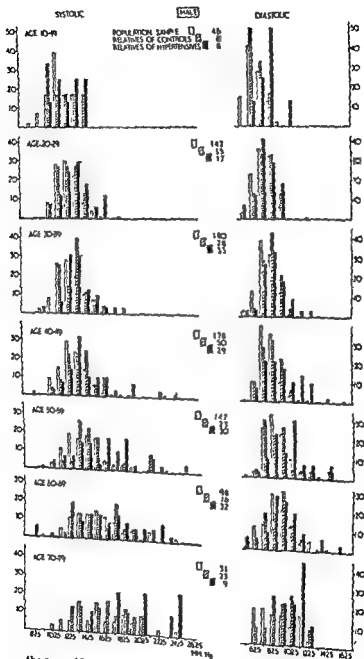
¹ First degree relatives

² In gene
who is term

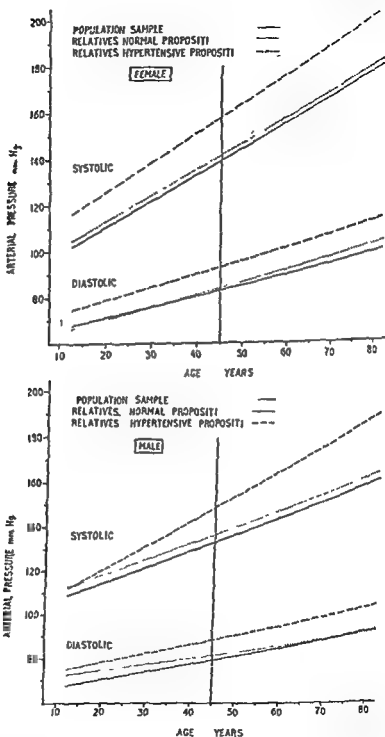
³ See pa



FIGS. 9.1 and 9.2 show the frequency distribution of systolic and diastolic pressures for females and males in the second to eighth decades of the three samples; the population sample (white rectangles), the first degree relatives of propositi without hypertension (hatched rectangles), and the first degree relatives of propositi with essential hypertension (black rectangles). The pressures are arranged in groups of 10 mm., and since



the range 100-109 contains only two readings 100 and 105 the mid-
102.5 mm. is shown on the abscissa



FIGS 9.3 and 9.4 respectively for females and males, show the regression lines of blood pressure on age for the relative normal (continuous line), the relative hypertensive (dotted line). The upper line is for systolic pressure, the lower for diastolic. (273.)

relatives compared. The conclusions to which these two methods of comparison lead is the same, namely, that the relatives of propositi with hypertension tend to have higher pressures at all ages from the second to the seventh, and possibly the eighth, decade. Thus, in any decade, the shapes of the frequency distribution curves are very similar in each of the three series, allowing for the effects of small numbers at the extremes of age. But whereas the curves for population sample and relatives of control propositi are almost superimposed, those for the relatives of propositi with hypertension are moved to the right; they begin at higher pressures, the modes tend to be higher and the top pressures recorded are higher. Similarly, the regression lines are parallel in the three series for both systolic and diastolic pressure in females and for diastolic pressure in males; male systolic pressure does, however, show a significant elevation in the rate of rise with age in the relatives of the hypertensive propositi. This parallelism, though at first sight rather striking, is, in fact, probably the resultant of two opposing processes which, as shown on p. 100, cancel one another out. All the regression lines of blood pressure on age of the relatives of hypertensive

Here, then, were the results which, from previous work we had anticipated.

Thus, from age from 0 in the youngest to over 50 per cent. in the oldest age groups. Thus we had found in our two control series the features which had been held to indicate dominant inheritance of hypertension. Those, such as Weitz and Platt, who have favoured the dominant gene hypothesis have assumed that the presence of its presence in the relatives of the propositi was the more characteristic of the inheritance. The more thought we gave to the problem, the more clearly it emerged that the question we had asked, and which others had asked before, was not a proper question, since the whole concept that essential hypertension was of its own was quite this question in the line, namely that essential hypertension was no more than that group of subjects, irrespective of age, whose pressures exceeded a certain value, defined on arbitrary grounds. This conclusion, which is

no more than a restatement of the facts, seems so obvious and so commonplace, that I feel almost ashamed to reiterate it. Yet I am convinced that a fundamental confusion of thought arose in my mind, and still arises in the minds of most workers in the field, through failure to recognize this elementary fact.

Genetic Analysis using the Age-adjusted Score

Having thus cleared our minds of what might, perhaps, be described as false dogma, we proceeded to a genetic analysis of the material so collected. In starting this analysis we adopted two tentative working hypotheses, based on the data already set out, namely:

(1) That the difference between essential hypertension and normality is quantitative and not qualitative, and there is no clear line of demarcation.

(2) That the genetic element in hypertension represents no more than a tendency for relatives to resemble one another in pattern of arterial pressure.

The most important step in the analysis was the devising and testing of a method of awarding a score for arterial pressure that adjusts for differences in age and sex, as described in the previous chapter. It will be remembered that this score assigns a plus or minus value for systolic and for diastolic pressure, the value indicating the extent of the deviation from the norm, all values being adjusted as for age 60. The use of this score allowed us to make comparisons between groups of individuals necessarily of very different ages.

In making this analysis we were fortunate in being able to use not only our own material but that collected by Soby (1948), who gives the blood pressures of the relatives of his hypertensive probands, though not of the probands themselves. The results for both our series of relatives, and for the relatives of Soby's probands with hypertension, are summarized in Table 9.1.

It will be seen that the relatives of the control probands yield scores that are not far removed from zero, though they tend slightly to exceed it¹ while the relatives of hypertensive probands, both our own and Soby's, are considerably raised. There is no significant difference between the three kinds of relatives, siblings, parents and children in either systolic or diastolic pressures of our series, or for diastolic pressure in Soby's series, though in his series the mean for systolic

¹ The same tendency may be seen in the regression lines of Figs. 9.3 and 9.4. Since the relatives of the control probands were selected on the basis of low arterial pressure, it might have been expected that their blood pressure would be lower than the general population, but this is probably due to the circumstances of measurement of blood pressure in relatives being less exact than those of the population sample. While the population sample were all investigated after a rest in the outpatient waiting hall, many relatives were investigated in their homes or in doctors' offices. The conditions were, however, identical for both series of relatives.

TABLE 9.1. *Comparison of Means of Sex- and Age-adjusted Scores for the various Groups of Propositi and Relatives (Hamilton and others, 1954c).*

	No	Mean Score in mm. Hg as at age 60	
		Systolic	Diastolic
I. Propositi			
Controls*	371	- 6.73	- 5.44
Hypertensives*	387	+ 95.00	+ 51.28
II. Relatives of controls			
Siblings	262	+ 4.56	+ 2.56
Parents	83	- 1.81	+ 1.87
Children	26	- 1.73	+ 1.73
Total	371	+ 2.70	+ 2.35
III. Relatives of Hypertensives			
A. Present series			
Siblings	267	+ 23.60	+ 12.40
Parents	63	+ 21.19	+ 12.38
Children	57	+ 20.83	+ 10.61
Total	387	+ 22.80	+ 12.20
B. Soby's series			
Siblings	468	+ 20.56	+ 13.23
Parents	47	+ 12.98	+ 9.15
Children	160	+ 10.03	+ 11.00
Total	675	+ 17.53	+ 12.41

* Each propositus is counted as many times as he has first degree relatives in the series

NOTES

1 Diastolic means for relatives of controls are homogeneous.

pressure in children is significantly lower than in siblings. Taking the material as a whole, it seems safe to conclude that when adjusted for age and sex, the mean systolic score for all his relatives is significantly

... of hypertensive propositi investigated by Soby and ourselves shows no significant difference in diastolic scores, though the mean systolic score for all his relatives is significantly

lower than ours. Considering the differences in country and circumstances in which the measurements were made, the agreement is surprisingly satisfactory. This agreement has added considerably to the confidence with which we approached the analysis of our own figures and has enabled us to add his rather larger series to our own for some purposes. Thus we found that the degree of resemblance between relatives of like and opposite sex was the same. The independence of sex so far as inheritance is concerned is another simplification, for it is unnecessary to separate fathers from mothers, brothers from sisters or sons from daughters.

The Estimation of the Degree of Resemblance between Relatives

The tendency of relatives to resemble each other may be expressed numerically by the regression coefficient or some equivalent statistic. If, say, the regression of first degree relatives on their propositi is 0.2, then for each rise of 10 mm. in the arterial pressures of the propositi, the pressures of their relatives will rise 2 mm. on an average. To test the validity of our two working hypotheses, we therefore calculated the regression coefficients on the material as a whole and separately on the two samples.

Our first calculations were made on the material as a whole. The simplest calculation divides the mean score of the first degree relatives in Table 9.1 by the mean score of the propositi, and gives values of 0.238 and 0.240 for diastolic and systolic pressures. These values may be too high since they assume that the relatives were measured under exactly the same conditions as the sample of the population from which the norms were calculated. To allow for this we therefore divided the difference in mean scores of the two sets of relatives by the difference in the mean scores of the corresponding hypertensive and control propositi. This gave regression coefficients of 0.174 for diastolic and 0.198 for systolic pressure.

We next calculated the regression coefficients of relatives on their propositi for each sample separately. This was a more complex procedure and was made by the use of a two-way table.

The Regression within the Control Sample. Within the control sample, the regressions were: diastolic +0.083, systolic -0.125. Neither of these differs significantly from zero, and there is thus no evidence that in the control series relatives resemble their propositi in arterial pressure. Nevertheless, there are reasons discussed in our original paper which lead us to conclude that a real positive association is not excluded.

The Regression within the Hypertensive Sample. Calculating the regressions from a two-way table, between propositi and their relatives, in the same way as for the control sample, the results are shown in

TABLE 9.2. *Diastolic Scores of Hypertensive Propositi with Corresponding Mean Scores of their Relatives (Hamilton and Others, 1954c).*

Propositi Score +	Relatives	
	No.	Mean Score +
10, 15, 20	44	3.86
25, 30, 35	86	12.97
40, 45, 50	99	11.97
55, 60, 65	64	15.47
70, 75, 80	41	15.85
85, 90, 95	35	11.14
100, 105, 110	15	6.39
115, 120, 125	1	
130, 135, 140	0	
145, 150, 155	0	
160, 165, 170	2	

Regressions :

Including propositi up to + 80 only + 0.161
 " " " + 95 only + 0.116
 " all propositi + 0.001

First two regressions are respectively highly significantly and significantly different from zero.

Table 9.2, where the propositi are arranged in groups of 15 mm., with the corresponding mean scores of their relatives. It will be noted that over most of the range, the mean scores of relatives increase as the scores of the propositi rise, until the latter reach +80, after which the scores of relatives fall, the fall becoming considerable when scores of the propositi exceed +95. The table suggests that over most of the range, the regression is compatible with the figure of +0.2, but that some of the highest scores may belong to individuals in whom a new factor intervenes, and who are, in fact, suffering from secondary rather than essential hypertension. The very high scores belonged in general to the younger propositi with very gross hypertension. The suggestion that some of them had a distinct lesion accounting for their high pressures, and were therefore cases of secondary rather than essential hypertension, recalls conclusions reached by Platt (1947) from different lines of enquiry. Platt concluded from his studies of family history that many of those who at first sight seemed to be suffering from essential hypertension, but whose family histories were negative, were in fact suffering from secondary hypertension. In a separate investigation into severe hypertension in young persons (Platt, 1948) he found that of 45 patients under the age of 40 years, only 13 could

be regarded as essential hypertension. While we excluded secondary hypertension by the routine methods currently employed, we are by no means satisfied that we were uniformly successful in doing so. Pyelonephritis is probably the lesion most commonly overlooked.

The Effects of the Age of the Propositi with Hypertension. When these observations began, we had not fully appreciated the effects of age on arterial pressure, and we did not take age into account in selecting propositi. In terms of age-adjusted score there was therefore a considerable difference between our younger and older propositi with hypertension, the younger propositi having much the higher scores. Table 9.3 shows the mean scores of propositi arranged in fifteen-year age groups, the corresponding scores of their first degree relatives, and the regression calculated by dividing the mean scores of relatives by the uncorrected mean scores of the corresponding propositi. As might have been expected from the method of selection,

TABLE 9.3. *Analysis by Age of Hypertensive Propositi (Hamilton and others, 1954c).*

Age of Propositus	No. of Propositi	Actual Mean BP Propositi	Mean AAS Propositi	No. of Relatives	Mean AAS Relatives	Regressions*	
						Systolic	Diastolic
20-34	20	190/110	136/70	61	23.7/14.3	0.21	0.20
35-49	49	214/129	111/68	171	25.0/13.7	0.23	0.24
50-64	34	225/129	87/45	126	20.0/10.6	0.23	0.24
65-79	7	200/118	26/24	29	10.3/ 6.2	0.40	0.26

* Between sample regressions obtained by dividing mean age-adjusted score of relatives by mean age-adjusted score (AAS) of propositi (unweighted).

the mean arterial pressures of propositi are not related to age, and accordingly their mean age-adjusted scores fall with age. But it will be noted that the mean age-adjusted scores of the corresponding relatives also fall, the regression remaining practically constant at a little over 0.2, except in the oldest group where numbers are small. This has happened despite the fact shown in Table 9.2 that a few of the youngest subjects with the highest scores were probably of a different group. It would seem then that the younger propositi, who have the higher scores, are suffering from a greater degree of hypertension, and that this is faithfully reproduced in the higher mean scores of their relatives.

The figures of Tables 9.2 and 9.3 are alone sufficient to rule out the hypothesis that the population can be divided into those with normal and those with high pressures. According to current usage all propositi have "essential hypertension," yet clearly there are degrees of hypertension, in fact a continuous distribution from mild

to severe. It is not simply a question of the mild case becoming severe with the passage of time, although, as we have shown, arterial pressure rises with age in the general population, and in the relatives of propositi with hypertension. There would seem, in addition, to be intrinsically mild and intrinsically severe cases, the intensity being reflected in the age-adjusted score.

The results given in Table 9.3 explain what would otherwise be an anomalous finding. A given deviation from the norm at age 20 corresponds to a much larger deviation at age 60, and yet Figs. 9.3 and 9.4 seemed to show that the pressures of the youngest relatives of propositi with hypertension are deviated from the norm to the same extent as are those of older relatives. The majority of the relatives

TABLE 9.4. *Sets of Siblings (Propositi Omitted). Variance Ratios of Mean Squares between and within Families, and E (analogous to regression coefficient) (Hamilton and others, 1934c).*

	No. of Families	No. of Individuals	Age-adjusted Scores			
			Systolic Scores		Diastolic Scores	
			Variance Ratio	E	Variance Ratio	E
Families ascertained through control propositi	70	257	1.52	0.123	1.38	0.092
Families ascertained through hypertensive propositi						
A. Present series.	73	276	2.39	0.268	1.95	0.109
B. Sebye's series.	184	605	1.89	0.213	2.00	0.232
C. Present series and Sebye's series combined	257	880	2.07	0.237	1.95	0.216

are siblings, and so resemble their propositi in age distribution. Thus the younger relatives are derived from the younger propositi and therefore depart more greatly from the norm as Table 9.3 shows. Hence curves which should have shown increasing divergence have become artificially parallel.

The Resemblance between Siblings. Since the propositi were selected on the basis of their blood pressures, and since the circumstances under which their blood pressures were measured were not the same as for the relatives, the preceding estimates of resemblance are not by themselves conclusive. However, these objections do not apply to estimates of the degree of resemblance between siblings, the propositi being omitted. The estimate made was an intra-class coefficient (E) that closely corresponds to the regression coefficient. The results are shown in Table 9.4.

It is satisfactory again to find that our own and Soby's relatives of propositi with hypertension yield such closely similar results, the differences in the variance ratios being less than their standard errors. Combining the two series gives 257 sets of siblings comprising 880 individuals, so that the estimates are relatively reliable. The resemblances between siblings can be expressed by regressions of slightly more than 0.2, which agree well with those obtained by the other methods.

Once again, however, the relatives of propositi without hypertension yield an equivocal result, for the degree of resemblance is just significantly different from zero for systolic but not for diastolic values. On the other hand, neither value is significantly different from the corresponding figure obtained for the siblings of the hypertensive series.

The Size of the Genetic Factor

These results show, we think clearly, that there is in fact a resemblance in the arterial pressures of close relatives, at least when those relatives are derived from a propositus with hypertension and, in the regression coefficient or correlation coefficient, they suggest what this degree of resemblance is. Unfortunately our numbers were insufficient to show whether there is a resemblance between close relatives derived from propositi with normal pressures, and, if so, whether this resemblance is quantitatively similar or different to that found in the hypertensive series. Miall and Oldham have recently investigated this important point and kindly allow me to quote their unpublished results. They took a 1 in 90 sample of population aged over five years of a Welsh valley (Rhondda Fach) as propositi. They measured the arterial pressures under similar circumstances on 137 males and 113 females who formed 98.6 per cent. and 92.6 per cent. of the propositi, and on 978 of the 1,005 first-degree relatives (97.3 per cent.) living within twenty-five miles. They found that the mean systolic age-adjusted scores of the six different sets of first-degree relatives (fathers, mothers, brothers, sisters, sons and daughters) of both male and female propositi did not differ significantly from one another. A single regression would describe the dependence of relatives on all kinds of propositi of either sex. The regression coefficient has a value of 0.239, standard error ± 0.032 . They found no evidence to suggest a deviation from linearity in this regression. The relationship between the systolic pressures of all first-degree relatives and that of their propositus is therefore independent of the level of arterial pressure of the propositus. This conclusion, derived from an investigation in which propositi were selected on grounds totally unrelated to arterial pressure, thus repairs the deficiency in ours, and shows that arterial pressure behaves as a

graded characteristic throughout the range, so far as inheritance is concerned.

Moreover, Stocks' (1930) observations show clearly that there is an inherited pattern for blood pressure in normal young children. He investigated 832 children, of whom 563 were members of twin pairs attending London County Council schools between 1925 and 1927. To compare children of different age and sex, he used a correction method closely similar to the age- and sex-adjusted score used by us. From these figures he obtained correlation coefficients. He argued, however, that these coefficients were too low, as they took no account of errors of measurement or of individual variability. He therefore made similar measurements daily for fifty days on five adults in his laboratory, and used those figures to apply approximate corrections to the correlation coefficients. The figures obtained for blood pressure (combining systolic and diastolic pressures) are shown in Table 9.5.

TABLE 9.5. (Stocks, 1930.)

		Number	Observed Correlation Coefficient	Calculated Correlation Coefficient
Opposite-sexed pairs	Twins . . .	101	0.26	0.34
	Others . . .	248	0.36	0.48
Like-sexed pairs	Other than twins	286	0.37	0.45
	{ Monozygotic . .	93	0.69	0.81
	{ Dizygotic . . .	85	0.32	0.44

Stocks goes on to give two estimates of the relative effects of constitution and environment. The first is Holzinger's (1929) :

$$T = \frac{\text{Mean difference in dizygotic-like sexed pairs minus mean difference in monozygotic twins}}{\text{Mean difference in monozygotic twins}}$$

The second is his

$$t^2 = \frac{\text{Monozygotic } r - \text{dizygotic } r}{1 - \text{monozygotic } r}$$

where r is the correlation coefficient.

These estimates are chiefly valuable in showing the relative contributions of heredity and environment to various characteristics. Stocks' figures were as follows :

Height	T	t^2
Weight	1.3	10.4
Blood pressure	1.4	7.0
Pulse and respiration rates	0.2	2.0
	0.1	1.0

So far as children are concerned, the point would therefore seem to emerge that, as compared with environment, heredity is of considerably less importance in determining arterial pressure than it is in determining height and weight. Unfortunately there are no comparable figures for adults, which are, of course, our main concern here.

The size of the genetic factor, as indicated by the correlation coefficient, emerges very differently from Stocks' work and ours. His highest coefficient (corrected) is for monozygotic twins and is 0.8; ours for hypertensive relatives is a little over 0.2. These would give approximate estimates for the contribution of heredity varying between 64 and 4 per cent., a disparity that forms an eloquent comment on the present lack of precision of our knowledge.

Even for oppositely sexed pairs of siblings of different ages, Stocks' uncorrected correlation coefficients are higher than ours. The most probable explanation for the disparity is that Stocks' subjects were all children, ours chiefly adults. This suggests that the relative contribution of inheritance decreases, while that of environment increases with age, a conclusion which might have been expected on general biological grounds.

One further calculation is of some interest. Our population sample showed that the proportion of persons having diastolic pressures of 100 mm. Hg or more at age 60 are: females 31.7 per cent., males 17.3 per cent. Assuming a regression of $+0.23$, the proportion to be expected amongst the first degree relatives of hypertensive probands similar to our own will be: females 61.7 per cent., males 47.2 per cent.; an incidence closely similar to that actually observed by Soby in his relatives. The figures show how modest a degree of genetic resemblance is needed to produce an apparently striking association when the line dividing normal and abnormal is drawn near that attained by the average person.

The Nature of the Genetic Factor

Within the upper ranges, arterial pressure behaves like a graded characteristic so far as inheritance is concerned. It seems probable, but is less securely established, that it behaves similarly throughout the range of arterial pressure. In this it broadly resembles height, but the rôle of inheritance is here much more definite, partly no doubt because height is very much less affected by momentary variations. This having been said, the conception of Mendelian dominant inheritance needs little further reference; it is unsupported. The inheritance is more probably multifactorial.

Although the concept that essential hypertension is inherited as a Mendelian dominant is thus dismissed, it is dismissed with great respect, for it is to be remembered that without this hypothesis, so

attractive in its stark simplicity, the observations here described would never have been made. Once again we find that the true function of hypothesis is to stimulate enquiry.

SUMMARY

Penetrating investigations into the role of the genetic factor in the inheritance of blood pressure

presented in this chapter indicate clearly that in the upper ranges at least arterial pressure is inherited as a graded characteristic. To what extent this is true of the lower ranges is not decided by our observations, though those of Stocks on children suggest that inheritance is concerned throughout the blood pressure range. A minimum value for the size of the genetic factor is expressed by a regression coefficient of 0.2; that is to say, if the arterial pressure of one member of a sibship is raised above the normal for that sex and age by 10 mm. Hg, the blood pressures of the other members will be raised on an average by 2 mm. Owing to the large diurnal variations in blood pressure discussed in Chapter 3, this estimate is certainly too low, but it is difficult to be sure how much too low. It would be no more than a guess to say that the genetic factor and diurnal variation together account for half of the deviations of arterial pressure from the norm encountered in the population at large. This would leave half to be accounted for by environmental factors. I venture to make these guesses, not because I have any grounds for believing they are, even approximately, correct, but to draw attention to the necessity for obtaining data from which more accurate estimates can be made.

CHAPTER 10

THE RÔLE OF ENVIRONMENTAL FACTORS IN THE GENESIS OF ESSENTIAL HYPERTENSION

As causes of disease, environmental factors have the inestimable attraction for the practising physician that they can usually be modified and often removed and so offer the way to a "cure." One might parody Voltaire's famous remark,¹ and say that if such causes did not exist, it would have been necessary to invent them. Almost every environmental factor has been hailed as the cause of hypertension, as of other diseases, and the enthusiasm with which the appropriate treatment has been adopted has varied with the popularity, for the time being, of that general hypothesis of disease. Discussions of environmental factors thus bear, more heavily than most, the imprint of the mental climate under which they were written. Unfortunately, however, the evidence for the participation of many of these environmental factors is slight or non-existent and, since they have been fully reviewed by Fishberg (1939), this account will be so much the shorter.

There are two general difficulties in the elucidation of the subject, the one inherent in the material, the other imposed by us through the tyranny of words.

It is clear from the evidence already presented that the blood pressure is affected basically by genetic factors and temporarily by the circumstances of measurement. In order to identify with certainty the influence of environmental factors, the contrasting groups should be genetically similar and should be examined under comparable conditions. For example, it has not proved possible to measure at, say, age 60-65, under comparable conditions groups that are similar in all other respects except that one has been doing light, and the other heavy work for many years. Moreover, were a difference found, would it be the result of environmental differences? Might there not be a constitutional factor itself related to blood pressure which determined the type of work taken up by the individuals themselves? For instance, according to Wolf and Wolff (1951), subjects with hypertension are more square and muscular than the average. Again, when we come to consider geographical factors, we shall find that not only race, but nearly every kind of environmental factor is different. It is not surprising therefore that, while the consideration of the part played by inheritance has suggested plainly the importance of environmental

¹ Si Dieu n'existant pas, il faudrait l'inventer.

factors in determining arterial pressure, little is known of their relative contributions.

The second difficulty is of our own making. It results from the introduction of a new word, or rather the transmutation of an old word, "*stress*," to indicate a common stage in the response to various environmental factors, and the subsequent easy transition in its usage to mean those environmental factors whose impact is largely on the mind. The reason for introducing the word is explained succinctly by Selye (1951): "In 1936, we demonstrated, by animal experimentation, that the organism responds in a stereotypical manner to a variety of widely different agents such as infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue, or X-irradiation. The specific actions of all these agents are quite different. Their only common feature is that they place the body under a situation of stress. Hence we concluded that the stereotypical response—which is superimposed upon all specific effects peculiar to the agent—represents a *reaction to stress*." In his recent book, "*Stress and Disease*," H. G. Wolff (1953) states "stress is the internal or resisting force brought into action in parts by external forces or loads. The change in size or shape of the machine

... stimulus agent. In the classical language of biology, a change in environment represents a stimulus, the resultant changes in the organism, which happen by virtue of its being a living creature, represent the response. Clearly, Selye uses stress to mean the first stage in the common response of the body to a large variety of agents, and in his concept of adaptation and the diseases thereof, stress seems to represent the process intervening between the environmental change and the activation of the pituitary. Wolff uses the word in the same sense but with a special meaning. "The stress becomes the interaction between external environment and organism, with the past experience of the organism as a major factor." Wolff has, of course, enormously advanced our understanding of the body-mind relationship in disease. His special meaning, therefore, relates to those special cerebral activities that are called the mind.

... in which it, or writers use the word in a special sense that distinguishes it from its ordinary sense (especially the word as used in the ordinary sense).

cine. Unfortunately, there was no word to designate those kinds of environmental factors which exert their effects through the mind, and so in contemporary medical writing stress has come to fill that void. Perhaps to the average person the distinction between stress and response is too slight to justify a new word. Perhaps its popular meaning has proved too strong. Since, however, there seems little doubt that its use is leading to utter confusion it will not be employed here.

Nevertheless, as we have seen, genetic factors are only in part responsible for the higher pressures that are the basis of essential hypertension. It is certain, therefore, that environmental factors are also concerned and possible that they play the major rôle. In searching for such environmental factors, it is natural to look with especial care at those which cause usually a rise of arterial pressure during the period in which they operate. It has been shown in Chapter 5 that hypertension induced in the experimental animal is less easily reversible when it has lasted a long, than when it has lasted a short, time. Similarly, it will be shown in subsequent chapters that persistent hypertension in man, associated with unilateral renal lesions (Chapter 17), coarctation of the aorta (Chapter 22), Cushing's syndrome (Chapter 21) and pheochromocytoma (Chapter 20), is not always abolished when the anatomical defect, that appears to cause it, is removed by surgery. There is, therefore, a background of established fact to make inherently reasonable the idea that repeated exposure to blood-pressure raising stimuli may eventually lead to a sustained rise of pressure that persists even though these stimuli have ceased to operate.

The idea that repeated exposure to environmental influences which normally raise arterial pressure eventually leads to a sustained hypertension has been particularly developed by Smirk (1949) and by H. G. Wolff and his colleagues. Wolff and Wolff (1951) regard hypertension as one of those diseases in which "the morbid process involves the unduly intense or sustained use of normal homeostatic adaptive patterns designed for phasic or short-term needs. The 'misuse' of such adaptive patterns has thus contributed to the pathogenesis of troublesome symptoms and disease states." This hypothesis would seem to me inherently probable.

ENVIRONMENTAL FACTORS IN WESTERN CIVILIZATION

Physical Exertion

In normal subjects the arterial pressure rises with physical exertion, and one might suppose that long-continued physical exercise may be a factor in inducing persistent hypertension. The circulatory changes induced by exercise are not, however, like those found in

hypertension, since the rise is largely due to increased cardiac output while the total peripheral resistance may fall. Taylor and others (1949) and Stevenson and others (1949) have found that moderate exercise does not elevate the arterial pressure more in subjects with hypertension than in normal subjects. Fowler and Guz (1954) found a greater rise than normal of arterial pressure in mild to moderate hypertension, but they also found that in severest hypertension, exercise may cause a fall of arterial pressure.

It is not common experience that hypertension is more prevalent in those doing hard physical work, and the greater rise of arterial pressure with age in women than in men, together with the common predominance of women in hypertensive clinics, is against the idea that physical exercise is an important factor in pathogenesis. However, evidence of this kind is of little weight. One of the few controlled investigations is that of Newnam (1952), who has compared the arterial pressures measured at the age of 60 in employees of British Railways who wish

relatively heavy. The mean arterial pressures in these two groups were respectively 168.75 systolic and 88.79 diastolic and 172.11 systolic and 89.26 diastolic, and statistical comparison showed no significant difference. While this work is not finally conclusive, since it is possible that those with the highest pressures might not have wished to continue employment and since the contrast in heaviness of work was not as great as might be desirable, yet it is probable that physical exertion is not an important factor in the genesis of essential hypertension.

Diet and Body Weight

Height. In adults blood pressure is not correlated with height (Faber, 1924; Huber, 1927; Master, Dublin and Marks, 1950).

High Protein Diet and Tobacco. Dublin, Fisk and Kopf (1925) reviewed the data obtained on 18,662 policy holders of the Metropolitan Life Insurance Company, examined in 1921 by the Life Extension Institute according to a standard plan. They found no significant difference in the percentage of hypertension in those taking a high protein diet and the remainder. They also found the differences in the percentages of hypertension were very slight as between excessive, temperate, and non-users of tobacco.

Obesity. The data

of Short and Johnson, 1939; Boynton and Todd, 1948). The figures of Master, Dublin and Marks (1950) are

representative. Dividing their subjects into 10 per cent. or more underweight, average, and 25 per cent. or more overweight, the relevant mean systolic and diastolic values for males age 20-24 were: 119.5/74.1, 123.7/75.4 and 126.2/82.2; and age 60-64: 139.2/82.6, 142.1/84.6 and 148.3/89.4. These differences, though quite definite,

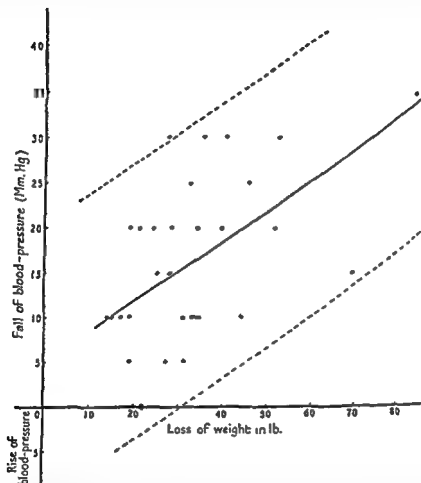


FIG. 10.1. Relation of fall in diastolic blood pressure to loss of weight in obese hypertensive women who lost weight on diet. Correlation coefficient, $r = 0.54$. Regression, $y = 0.327x + 5.7$. Black line is the regression; the dotted lines the 95 per cent. confidence limits (Fletcher (1954), *Quart. J. Med.*, 23, 331).

are not large, and it is possible that they may be accounted for by the error introduced by varying arm circumference to which Ragan and Bordley (1941) drew attention (see Chapter 2). This question could be answered, but this has not been done.

Nevertheless there are two reasons for supposing that the relationship between high blood pressure and obesity is more than a systematic error in the measurement. In the first place, reduction in weight by dieting may produce considerable falls of arterial pressure when it is initially high (Terry, 1923; Preble, 1923). Fletcher (1954) observed

who lost at least 14 lb. in weight. The pressures in the obese hypertensive women averaged 196/116 at the beginning and 163/99 at the end of the experiment. The changes in systolic blood pressure expressed as percentages of initial were in the three groups, -17.1 , $+0.6$, -4.3 , respectively. The fall of arterial pressure in the obese

TABLE 10.1. *Percentage of Persons in each Age Group showing Systolic Blood Pressure 20 mm. Hg or more above Average or Normal for Age (Dublin, Fisk and Kopf, 1925).*

Age Division	Overweight + 20% or more of Average (a)	Normal Weight within $\pm 5\%$ of Average (b)	Difference (a-b)	Odds in favour of Inherent Relation
All ages	15.7	6.1	+ 9.6	Practical certainty
Under 25	5.1	5.6	- 0.5	Sample inadequate
25-34	11.2	4.5	+ 6.7	Over 20,000
35-44	10.7	4.0	+ 6.7	Over 16 million
45-54	22.4	8.2	+ 14.2	Over 730 million
55 and over	32.0	23.1	+ 8.9	32

hypertensive women was much greater than could be accounted for by change in arm circumference as estimated by applying the correction given on p. 22, or assessed by the change in group 3. The relationship between fall of blood pressure and loss of weight is shown in Fig 10.1. In the second place, the figures of Dublin, Fisk and Kopf (1925), quoted in Table 10.1, show that the percentage of persons, having blood pressures 20 mm Hg or more above the norm for that age, increases more rapidly with age in the group that is 20 per cent. or more overweight, than in those whose weight is within 5 per cent. of the average. These two considerations reinforce the point made by Kahler and Weber (1940) in suggesting that overeating may be a contributory factor to the development of the higher pressures. This evidence is very far from conclusive, but it is sufficiently suggestive to be worthy of careful consideration.

Semi-starvation. In the so-called Minnesota experiment, Keys, Henschel and Taylor (1947) subjected 32 young male volunteers, age 20-33 years, to controlled starvation for six months, sufficient to reduce their body weights by one-quarter. The diets were those common to large populations in time of shortage, and consisted largely of coarse cereals and potatoes, bulk being provided by cabbage and turnips. Meats, fats and dairy products were present in token amounts only;

no vitamins were added. The changes in blood pressure found during twenty-three weeks of such a diet and after twelve weeks of rehabilitation are shown in Table 10.2. During the period of semi-starvation, heart size decreased by 16 per cent. of its total volume ; this recovered during the period of rehabilitation.

Similar changes were observed during the starvation in the last Great War in Europe. Lups and Francke (1947) measured the blood pressures of 520 patients aged 20 to 75 years in April, 1945, at the height of the food shortage in Holland when, 80 per cent. of them had lost 20 per cent. in weight. They compared these figures with those taken at earlier visits before the food shortage. In April, 1945, the

TABLE 10.2. *Mean Values for 32 men for Pulse Rate and Blood Pressure (mm. Hg) in Control Period and after 5, 13, 20 and 23 weeks of Semi-starvation and after 12 weeks of Rehabilitation. All Measurements were made in Basal Rest (Keys, Henschel and Taylor, 1947).*

	Control Period	Weeks of Semi-starvation				Rehabilitation Period
		5	13	20	23	
Body weight, kg.	69.39	63.33	56.60	53.88	52.83	58.76
Pulse rate .	55.19	40.78	35.31	36.75	37.31	49.66
Systolic B.P. .	106.53	106.03	99.19	98.47	94.69	99.91
Diastolic B.P. .	69.91	68.46	68.22	70.47	64.50	68.25
Pulse Pressure .	36.62	37.57	30.97	28.00	30.19	31.66

pressures for each decade had fallen substantially, e.g. age 20-30 from 132/77 to 125/70, and age 60-75 from 164/88 to 144/76. However, further measurements in September, 1945, when over 80 per cent. of the population had experienced a considerable gain in weight, showed a rise of pressure in 43 per cent., no change in 13 per cent. and a fall in 44 per cent. ; that is the increase in weight was unaccompanied by an increase in arterial pressure. Mollison (1946) observed an average arterial pressure of 91/60 in 12 emaciated patients in Belsen Concentration Camp. Stapleton (1946) observed transient oedema, hypertension and proteinuria in Australian prisoners-of-war from Singapore after liberation and the administration of a liberal diet. The same tendency to increased arterial pressure is said to have occurred in Leningrad after the siege was lifted and starvation gave place to plenty (Brozek, Chapman and Keys, 1948). Neuprez (1945) found that, during the German occupation of Belgium, the body weights and the blood pressures of outpatients were alike considerably lower in 1941 than 1940, systolic and diastolic being each reduced about 20 mm. for a loss of weight of 10 kg.

Environmental Factors that Operate through the Mind

In the past the possible influence of the mind in the production of disease was either overlooked or, at least, rather quickly dismissed. To-day the idea that essential hypertension is a psychosomatic disease and therefore arises chiefly through the agency of the mind has many adherents. In trying to assess the evidence for this hypothesis two points should be very carefully borne in mind. The first is that, as we saw in Chapter 3, the arterial pressure is very dependent on the emotional state of the subject at the time of measurement. We should naturally expect, on the one hand, that subjects who are anxious or agitated would have higher pressures than those who are not so, and, secondly, that if this emotionally charged state is abolished, the arterial pressure will fall. These facts do not, however, imply that essential hypertension arises chiefly or in part through the agency of the mind. Nevertheless there are certain reasons which make it probable that the environmental factors, for which we are searching as major causes of high pressure, are those which operate through the mind. As we saw in Chapter 3, these factors are amongst the most potent in temporarily elevating blood pressure; and most of us know from experience how long the affective states of mind so produced can last. With these considerations in mind, we may consider the evidence.

(1) *The Blood Pressure in the Psychologically Ill.* Hall (1927) measured the arterial pressure in 53 patients with neurasthenia and psychasthenia. As normal he took for systolic 120, plus one-fifth age from 20 to 60, and for diastolic 80 at age 20, plus 1 mm. for each five years. Eighty-five per cent. of the patients had pressures below and 15 per cent. pressures above his normal figures, those with supra-normal pressures were generally agitated and the pressure fell to normal limits when the cause was removed. McFarland and Huddleson (1936) measured pressure in 160 patients in the wards of the Neurological Institute at Columbia University, New York, and 100 in the Psychiatric Institute, and compared them with controls.

of the controls and patients with anxiety state and neurasthenia, anxiety hysteria, conversion hysteria, mixed

pressure.

(2) *Is the Onset of Hypertension related to Psychological Events?* Reiser and others (1950), in an extensive investigation into 230

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strained aggression. Ackerman (1950) noted reactions in the personality repressing responses to danger, while Saul (1939) regarded hostility and unexpressed rage as the dominant characteristics of the hypertensive personality. On the other hand, Weiss and others (1952) found in a series of 150 unselected consecutive patients from the hypertensive clinic, that hypertension occurred in all types of personality from normal to psychotic, but that there was a great preponderance of neurotic personalities with a strong compulsive trend. Saslow and others (1950) made personality studies in 50 non-psychotic subjects with essential hypertension, 50 matching non-hypertensive psychiatrically ill patients, and 50 non-psychotic subjects without hypertension, but with chronic diseases not attributable to a disorder of the mind. As between the first and third groups, they found the largest correlations between the presence of hypertension and subnormal assertiveness, obsessive compulsive behaviour, and anxiety. While they pointed out that the positive associations between personality rating and hypertension did not signify an aetiological relationship, they suggested (a) that persons with the implied make-up are recurrently and frequently inhibiting impulses to overt action, (b) that blood pressure rises occur in some of these persons at such times, (c) that in time the blood pressure rises outlast the duration of the inhibited impulses, and finally, that hypertension is sustained instead of intermittent. Harris, Sokolow, Carpenter, Freedman, and Hunt (1953) investigated the personalities of 40 women undergraduates who, at initial physical examination, had blood pressures which exceeded 140 systolic or 90 diastolic, and 40 women whose blood pressures were less than 120/80. The psychiatrist interviewed 18 of the high, and 20 of the low, pressure group and, though ignorant of their arterial pressures, identified personality features which he had observed in essential hypertension in six of the low as compared with 12 of the high pressure group. The women were then each asked to play a part in a drama in which a difficult psychological situation occurred, the other part being taken by a staff member. The observers then recorded their impressions of each subject by selecting suitable adjectives from a list of 389. The adjectives chosen for the high pressure group suggested an unfavourable personality, e.g. "obnoxious," an inadequate control of behaviour, such as "unstable," an egocentric person, "stubborn," and moodiness, e.g. "resentful." "It is suggested, therefore, that the pre-hypertensives are less well able than normal persons to handle stressful or frustrating situations . . . without becoming emotionally upset, and that therefore they are more likely to be . . .

accompanied

Such . . .

work

"unselected" patients with hypertension, found that the correlation between "meaningful life situations" and the onset of symptoms and complications of hypertension was only 9 per cent. in 92 patients surveyed only medically, but rose to 100 per cent. in a group studied psychiatrically. On the other hand, Weiss (1942) in 93 patients found only five in whom psychic factors seemed inherently related to the onset of hypertension, and apparently an important factor in its development. In a later paper, Weiss and others (1952) make this pertinent remark: "So often we cannot tell whether the high blood pressure did not precede the symptoms which led to its discovery." This was very much Weitz's (1923) opinion; he regarded psychological and other factors as not being so much concerned in the genesis of hypertension as being the means of taking the patient to the doctor. On the other hand, Sokolow (personal communication) has found that the onset of the malignant phase of hypertension, which, as we shall see later, usually implies an exacerbation of the hypertension, is not infrequently precipitated by psychological situations with a very high emotional charge.

(3) *Is Hypertension associated with a personality Defect or Specific type of Personality?* This is, unfortunately, a most difficult question to answer. Most of the methods used are highly subjective, and the personality revealed by the tests may be a product of the mind of the research worker at least as much as that of the patient. It is tempting to suppose that some of the discordance of the results in hypertension and other conditions may be due to the hypotheses which dominate the minds of the investigators. Moreover, many of the tests were designed more for the investigation of organic mental disease than for the kind of disturbance of the mind that is envisaged here. Alexander produced the concept that every psychic tendency receives adequate bodily expression. Grace and Graham (1952) sought by interviews with patients to define what the patient "felt was happening to him, and what he wanted to do about it, at the time of the occurrence of the symptom." They found diarrhoea "occurred when an individual wanted to be done with a situation or to have it over with, or to get rid of something or somebody." "Constipation occurred when an individual was grimly determined to carry on even though faced with a problem he could not solve." "Arterial hypertension occurred when an individual felt that he must be constantly prepared to meet all possible threats." As they pointed out, the attitude can be considered as a description of the psychological process with which it is associated. Klein (1948), on the other hand, found that "specific gastro-intestinal illness cannot be correlated with any one personality type." Wolf and others (1948) found that 58 subjects with hypertension met threats arising out of problems of day-to-day living with an attitude of re-

(5) *The Effects of Psychotherapy and Leucotomy.* Psychotherapy will be further discussed in Chapter 15. Here it may be stated that many people seeking medical advice need a sensible discussion of their personal problems, and the implications of any disease present; this is particularly true of hypertension owing to the alarm that it so frequently arouses. The beneficial effects of sensible superficial psychotherapy are everywhere admitted by sensible folk. Wolf and Shepard (1930) found that the relatively free expression of aggression would reduce arterial pressure, sometimes by large amounts and for long periods. Weiss and others (1952) state, however, "While the symptoms that occur in patients with hypertension respond readily to psychotherapy, the blood pressure is less amenable, and we have no evidence that the course of the hypertensive vascular disease can be influenced by psychotherapy, no matter how intensive or prolonged."

Single cases in which the blood pressure showed a sustained reduction following prefrontal leucotomy have been observed by Tibbetts (1949) and Groen (1951). On the other hand, Chapman and others (1950) found that in 10 patients with essential hypertension in whom frontal lobotomy was performed, the principal effect was only a temporary lowering of systolic pressure. The response to immersion of a hand in ice-water was unaltered. In view of the failure, in some cases, of excision of a unilaterally diseased kidney, or phaeochromocytoma, or of repair of coarctation, to lower blood pressure, this negative evidence is inconclusive.

(6) *Is the Arterial Pressure unusually High in Subjects previously subjected for Long Periods to Anxiety and other strongly affective States of Mind?* Fraser and Cowell (1919) noted that among soldiers engaged in the actual fighting the blood pressure was higher than among men of the same regiment in support, but that the blood pressure tended to drop quickly when the soldier was away from the fighting line. Ehrström (1945) noted higher pressures in Finnish soldiers in the front lines than during peace. Ruakin and others (1948) observed diastolic pressures of 95 and over in 103 of 180 casualties from a vast explosion in Texas City, as compared with similar pressures in only 34 per cent. of surgical patients in the previous two months. But the really important observations from our present point of view, are those of Graham (1945), who measured the arterial pressure in 695 men of all ranks aged 20 to 38, who had spent at least a year, and mostly two to three years, in desert warfare in an Armoured Brigade. At the time of measurement, they had been in a training area in Tripolitania where conditions were good, for four to eight weeks after the battle had ceased. The means found were systolic 154, diastolic 90, 187 men having pressures exceeding 100 mm. Hg. More observations of this kind over a longer period are urgently needed. It would, for example, be

(4) *The Reaction of Normal Subjects and Subjects with Hypertension to Psychological Stimuli.* Extensive investigations have been made by Wolf and Wolff (1951) and their colleagues into the cardiovascular responses to various kinds of psychological stimuli introduced by conversation. The interviews fell into various categories. In the two unpleasant types, the subject might feel himself menaced or trapped, or he might feel defeated or overwhelmed. Twenty-one subjects with hypertension and 16 of the normal subjects displayed the first type of response and with it a rise of blood pressure, averaging 17 mm. (13.7 per cent. of the initial) in the former, and 8 mm. (8.9 per cent. of the initial) in the latter. In separate observations in which cardiac output was "measured" by the ballistocardiograph, unpleasant interviews in which the subject freely expressed his feelings, were found to be accompanied by a rise in cardiac output, rather less in the subjects with hypertension than in the normals, and a variable effect on peripheral resistance. It was more characteristic of the hypertensive group, reacting to the interviews by feeling menaced or trapped, not to show obvious external change but to display a calm and unruffled exterior; in such responses cardiac output was little affected, but the peripheral resistance rose in both normal subjects and subjects with hypertension. Finally, in further observations, they showed that in such interviews the glomerular filtration rate remained unchanged, while renal plasma flow fell with a consequent rise in filtration fraction. The renal vasoconstriction, as gauged by calculations of renal vascular resistance, was both more intense and more prolonged in the subjects with hypertension. Lumbodorsal sympathectomy was found to have little effect on the rises of blood pressure produced by such interviews but to abolish entirely the renal vasoconstriction. In one subject, injection of sodium amytal induced relaxation and "pleasurable phantasies" during which arterial pressure fell and renal plasma flow, glomerular filtration rate and filtration fraction all rose. This observation, they think, suggests "that the subject with essential hypertension may well be living in a sustained state of overreaction to the minor stresses of daily life."

Two of the hypertensive and six control subjects showed during interview a response of the second type with an attitude of being overwhelmed. In each instance the blood pressure fell and in one subject with hypertension a cold pressor test induced a fall of arterial pressure.

Wolf and Wolff conclude from this study that hypertensive subjects were "chronically in a state of conflict in which they felt a strong need to repress their aggressive drives and to gain approval by maintaining peace. They differed from normotensive subjects, many of whom displayed a similar reactive capacity, by invoking more or less continuously the pressor pattern referred to."

those in active service and free from disease known to affect blood pressure. Illustrative results are shown in Table 10.3. These results differ from American and British figures in two respects: the blood pressure is lower at all ages, and the increase in mean value and in standard deviation with age is much less conspicuous. However, Foster (1927) and Tung (1927) have shown that the blood pressures of Americans and Europeans, a year after residence in China, are generally significantly lower than they were before leaving home. They discuss, climate, diet and physical exercise as factors, and ascribe the change to the slower tempo of life in China. While it is also possible that the figures measured before leaving home were artificially raised by the implications of that examination, this criticism probably does not apply to the figures of Roddis and Cooper (1926) who found the systolic figures of 16 American Naval officers averaged 9 mm. lower in the tropics than after their return to northern waters. Similarly, Foster's measurements on 120 western men and women, mostly Americans, showed distribution curves intermediate between those of the local Chinese and those obtained by Alvarez (1923) on university entrants. Conversely, Krakower (1934), has stated that the blood pressure of Chinese long resident in Canada approximates to that of other Canadians and that essential hypertension is common amongst them.

Evidence from the Philippines (Chamberlain, 1911) and from Egypt (Ismail, 1928; Alam and Smirk, 1943) is rather conflicting. Cullumbine (1953) measured the blood pressure in 20,000 inhabitants of Ceylon sampled by the Department of Statistics. He found the average blood pressure of males aged 20 to 25 was 105 systolic, 60 diastolic, and that there was no significant rise with age.

However, by far the most interesting and important evidence concerns the African negro, since so many of their descendants form a part of contemporary western civilization in the North American continent. There is fairly general agreement that essential hypertension, in both its benign and malignant phases, is commoner in the coloured than in the white population of America (Allen, 1931; Flaxman, 1934; White, 1944; Fishberg, 1939). This difference, again, seems to extend to the population at large. Thus Adams (1932), in an eleven-year experience as medical officer to an undertaking employing over 5,000 men aged 18 to 65 in New Orleans, obtained records of 8,000 white and 6,000 coloured men, on application for employment, or at the annual examination. A recent study of figures is given in Table 10.4.

extremely interesting to compare the blood pressures on entry to the Forces, after, say, one to five years' active service and five years later in fighter pilots, bomber crews and ground staff of the Air Force. Observations of this kind might give a new understanding of our problem.

Comment. Reviewing this evidence as impartially as I can, I conclude that the extent to which environmental factors, operating through the medium of the mind, are important in producing high blood pressure remains an entirely open question. There is nothing inherently improbable in the idea. At the same time there is nothing conclusive about the evidence. The problem is one of the most difficult, because it is so complex and our methods of investigation so imperfect and of such doubtful accuracy. There would seem to be three lines of attack; to investigate established cases with proper controls by methods whose inherent error and whose observer error have been estimated; to follow other subjects over a lifetime to see to what extent prediction is fulfilled; and to measure the blood pressures of two populations, one of whom has been exposed for long periods to difficult psychological situations and the other not, but which, in other respects, are comparable. It seems very improbable that a final answer will be obtained without very careful and laborious work.

GEOGRAPHICAL FACTORS IN RELATIONSHIP TO ARTERIAL PRESSURE

Much information is available concerning the blood pressure levels in Asian and African peoples and this has been used in support of various genetic and environmental hypotheses. As we shall see, however, its interpretation is difficult. Moreover, some of the older observations were made with aneroid sphygmomanometers and are therefore of doubtful accuracy.

The blood pressure of Chinese in China has in general been found lower than that of Europeans or Americans in their native lands by Cadbury (1922), Kilborn (1926) and Tung (1930). Tung measured the arterial pressure on 1,223 males chiefly of the working and clerical classes employed in Peiping Union Medical College, and included only

TABLE 10.3. *Systolic Blood Pressure (mm. Hg) in Clerical Male Employees of Peiping Union Medical College (Tung, 1930).*

Age range . . .	20-24	30-34	40-44	50-54
Number . . .	313	194	77	26
Mean . . .	101	106	109	113
S.D. . . .	11.9	12.9	12.7	17.9

being used as index) are shown in Table 10.5. It will be noted that these figures are not very dissimilar from those of U.S.A. and Europe, and that the incidence of hypertension rises with age.

These results have been very differently interpreted. Some have used them as evidence that hypertension is due, at least in part, to the

TABLE 10.5. *Percentage of Bantu Subjects with Diastolic Pressures (Fifth Phase) over 90 mm. Hg (Ordman, 1948).*

Age	Male %	Female %
Under 20 .	8.2	5.8
20-29 . .	8.5	7.1
30-39 . .	18.0	15.7
40-49 . .	30.2	38.4
50-59 . .	37.0	30.8
60-69 . .	42.1	44.9
70-79 . .	27.8	41.5
80+ . .	6.9	37.6

intake of salt, others have thought protein was responsible, and most (e.g. Schulze and Schwab, 1936 ; Master, Garfield and Walters, 1952) that psychodynamic factors are important in producing hypertension in the American negro. But I would urge, as eloquently as I can, that the facts are much too complex to justify any conclusion, even a tentative one, though they are stimulating enough to provoke further observation. In addition to the factors just mentioned there is another which is generally overlooked, namely, the effect of infections and infestations which are almost universal in the native inhabitants of some tropical countries. In Chapter 7 it was pointed out that

TABLE 10.6. *Principal Causes of Death in Ceylon and Western Countries (per 1,000 deaths) (Cullumbine, 1953).*

	Ceylon		Euro	U.S.A.	England and Wales
	1945	1949	1947	1947	1947
Malaria and Pyrexia	167	82	—	—	—
Infantile Deaths	128	154	57	46	30
Respiratory	118	114	19	6	12
“	57	72	365	688	474
“	6	10	90	132	155

Africa and there are, unfortunately, few figures from these parts. In East Africa, the pressures of African natives tend to be lower, and to show little or no rise with age, and essential hypertension is uncommon, though hypertension secondary to urogenital lesions is not uncommon (Williams, 1944). A great difficulty in these observations is that the Africans have very inaccurate information of their ages. Donnison (1929) measuring the pressures of male recruits for labour and of older men gathered together in council in Kenya, obtained mean systolic and diastolic pressures of 123/82 at age 15-19, 125/86 age 35-39, and 107/70 at age 55-59. He used an aneroid manometer "tested

TABLE 10.4. *Systolic and Diastolic Blood Pressures (mm. Hg) in White and Coloured Employees of a New Orleans Industry (Adams, 1932).*

Age	Average S.B.P.		Average D.B.P.	
	White	Coloured	White	Coloured
21-25 . .	121	127	80	82
41-45 . .	123	131	83	89
61-65 . .	139	148	92	96

against another sphygmomanometer that was known to be accurate." He sought basal figures, discarding those in which no constant reading could be made. Williams (1941) using a mercury manometer and also repeating readings until a steady figure was obtained, got the following average systolic and diastolic averages for men: age 16-20 120/74, age 31-40 126/79, and age 51 and over 127/75. He also gives distribution curves. Clearly at the lower ages the results are not very dissimilar from those of Adams in New Orleans, but there is no evidence from the means, or the histograms, of any rise with age. On the other hand, in the South African Union, hypertensive heart disease is common amongst the native or Bantu population. Ordman (1948) measured with a mercury manometer the arterial pressure in 708 males and 814 female Bantus, mine workers returning from their shift, labour recruits, women from an antenatal clinic and rural Africans in Cape Province, Natal and Zululand. He found no racial or tribal correlation between those with raised diastolic (over 90 mm.) and normal pressures in any of the groups, though hypertension was correlated with excess body weight. Hypertension was not uncommon in the older Bantus in the rural districts, though it would seem that many of these had worked in their youth in the mines or in towns. His figures for the incidence of diastolic pressures over 90 mm. Hg (the final fading of the sounds

CHAPTER 11

ARTERIAL CHANGES IN HIGH BLOOD PRESSURE

In this chapter we deal with the structural changes found in the arteries in patients with high blood pressure. As we shall see in later chapters, these arterial lesions are of the very greatest importance in determining prognosis, and the location and kind of major disorders of bodily function that occur.

The importance of arterial lesions in high blood pressure has long been recognized. The pioneers, v. Basch and Huchard, in fact, spoke of hypertension as "latent arteriosclerosis" and "pre-sclerosis." In Allbutt's book, "Diseases of the Arteries" (1915), hyperpiesia was considered as a part of arteriosclerosis, although Allbutt recognized by his adjective, *decreascent*, that arteriosclerosis might occur without hypertension. Janeway (1913) spoke of "hypertensive cardiovascular disease." In the 1920 edition of Osler's "The Principles and Practice of Medicine," hypertension was considered in the section on arteriosclerosis. Such a tendency to identify hypertension with structural disorders of the arteries produced the first great obstacle to understanding the part played by organic vascular changes in the natural history of maladies associated with raised arterial pressure. For this identification led many to suppose, either that hypertension and the anatomical changes seen in the vessels were merely the functional and histological aspects of the same vascular change, or else that hypertension and arteriosclerosis were related as cause and effect, though opinions differed as to which was cause and which effect.

The second great obstacle, which is still commonly erected to obstruct the student, is the term *arteriosclerosis*, which is so all-embracing that it means little more than non-inflammatory disease of the arteries. We find it applied, for example, to non-syphilitic aneurysms of the aorta, the consequences of degenerative change in the elastic fibres in the medial coat of the aorta; to atheroma, a lipid deposit in the intima of aorta and large arteries; and to the changes visible with the ophthalmoscope in tiny arteries, about 100μ in diameter, in the retina, conditions which differ in almost every respect.

It is therefore necessary, in this account, to attempt to classify the lesions of the arterial system, and to try to relate them, so far as can be done, to raised arterial pressure. An attempt will be made to deal separately with vessels of different size, since the lesions affecting large arteries, on the whole, differ from those affecting small, also to separate

fever is very potent in reducing the intensity of hypertension, and it is at least possible that repeated fevers prevent the rise of pressure with age. To exemplify the importance of this factor, Table 10.6 shows the difference in death rates from some of the major causes in Ceylon, Eire, U.S.A. and England and Wales.

SUMMARY AND CONCLUSIONS

In Chapter 8 it was noted that arterial pressure tended to rise with age and that it rose more in some subjects than others. In Chapter 9 it was concluded that arterial pressure was in part genetically determined, but it was found that the rate of rise of blood pressure with age was not, on an average, greater in the relatives of propositi with high pressures than in the relatives of propositi with low pressures. By exclusion, it was suggested that environmental factors play a considerable, if not the major, part in determining arterial pressure, and it seems not unlikely that they are the chief determinants of the rate of rise of pressure with age. In this chapter the more obvious environmental factors have been considered; of these, the most important would seem to be those that operate through the mind, and diet. While the data are obviously quite compatible with the important rôle of such factors, they are, in general, much too complex to permit exact conclusions as to what the factors are and how much each commonly contributes to the deviations of arterial pressure from the norm. It is the essence of a scientific experiment that only one factor is varied at a time, so that the effect of that factor can be assessed. In this kind of epidemiological work, we are necessarily dependent on social and economic factors to provide such environmental change, and it is difficult to find groups which are strictly comparable in all other respects. Nevertheless, there probably are such groups whose careful comparison will unravel the tangled skein with which we have tussled in this chapter.

Affections of the Media

Hypertrophy of the Media

with
occurs
ates:

"Hypertrophy of the media of the muscular arteries is constantly associated with persistent elevation of the blood-pressure. I have obtained some evidence that a certain degree of hypertrophy of the media of the elastic arteries is also associated with heightening of the blood-pressure." "The degree of hypertrophy in the heart and the arteries is so closely related that it is possible to form an approximate estimation of the increase in the weight of the heart from microscopic examination of the arteries." "We also state that..."

hypertrophy was the chief component of the increased thickness of the arterial wall relative to lumen demonstrated by Kernohan, Anderson and Keith (1929) in biopsy of the pectoral muscle from patients with hypertension; in measurements on necropsy material, Morlock (1930) showed that a similar hypertrophy is found in arterioles of pancreas, liver, gastro-intestinal tract and spleen. Medial hypertrophy is, however, not invariable in hypertension, as was noted by Gull and Sutton (1872). As Fishberg (1927) and Bell and Clawson (1928) found, extensive elastosis and intimal proliferation or hyalinization may be associated with atrophy of the media. Vessels so affected would seem to have lost their contractibility.

Medial hypertrophy of systemic arteries was found by Goldblatt (1938b) in his dogs with hypertension produced by renal artery constriction. The nature of the change, the human evidence and the experimental evidence, all suggest that medial hypertrophy, like cardiac hypertrophy, is a work hypertrophy. It is one of the most suggestive pieces of evidence that active vasoconstriction, more or less generalized in the systemic circulation, is at least a factor in hypertension. Medial hypertrophy has been found in essential hypertension (Kernohan, Anderson and Keith, 1929) and in chronic nephritis (Fishberg, 1927). It was not found in skin or muscle from ... in five cases of ... was slight and White

Degeneration of the Media

(a) *Fatty degeneration* is often associated with atheroma, the fat occurring as small granules in the zone of media immediately external

lesions *morphologically distinct*. Such an attempt can only be partly successful, since vessels vary continuously in size, and since the actual lesions found in a given vessel are often a combination of more than one type of change. So far as large vessels are concerned, the classification is based especially on that of Turnbull (1915). It conforms, more or less, to the views of Jores (1904), Loehlein (1917), Volhard and Fahr (1914), Fishberg (1939) and Bell and Clawson (1928) for the smaller vessels.

CLASSIFICATION OF ARTERIAL LESIONS; THEIR DISTRIBUTION IN NORMAL SUBJECTS AND IN SUBJECTS WITH HIGH ARTERIAL PRESSURE

LESIONS AFFECTING THE LARGE ARTERIES, INCLUDING THE AORTA

The vessels comprised in this group vary considerably in structure and function. The aorta and its larger branches, such as the femoral and carotid arteries, have medial coats containing a preponderance of elastic tissue, and function chiefly as elastic receptacles converting the discontinuous stream, ejected from the left ventricle, into the continuous though pulsating stream through the arterial tree. As the arteries divide and decrease in calibre, muscle becomes a more and more important constituent, until the finest vessels lose their muscle coat and become capillaries. The smaller arteries and arterioles are, however, excluded from this section and will be considered separately later. The muscular arteries and the arterioles, have as their chief function the control of the peripheral resistance, and of organ blood flow.

It may therefore be surmised that these two sets of vessels will show lesions having different associations with raised pressure. Pathological processes, which lead to degeneration of the elastic fibres of the media of the aorta and large arteries, lead to an increase in pulse pressure. Existing alone they therefore give rise to the systolic hypertension noted on pages 46 and 128. Such changes are partly a function of age; therefore at any given diastolic pressure, the pulse pressure tends to be higher as age advances. On the other hand, the elevation of both diastolic and systolic values, which is the main theme of this book, is to be referred to changes, either functional or structural, in the muscular arteries and arterioles that comprise the major part of the peripheral resistance. It might, therefore, have seemed more sensible to separate the elastic and muscular arteries in the following account. This, however, would have been presumptuous of one who is not a morbid anatomist and I, therefore, follow accepted practice.

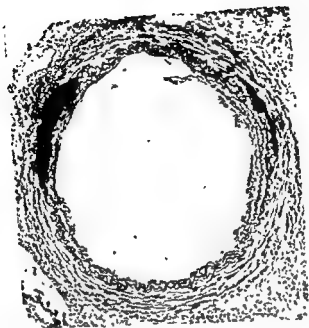


FIG. 11-1 ($\times 120$) Calcification of the media. Mönckeberg's sclerosis. The first lamina appearing black, in the media, just

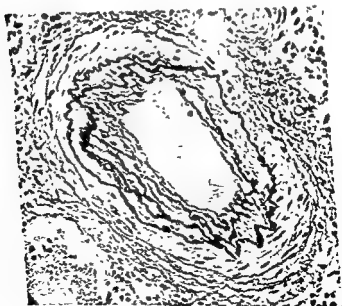


FIG. 11-2 ($\times 260$) Elastosis of small renal artery. Note the fragmentation of the internal elastic lamina into three to five concentric layers resulting

to the affected intima. It is especially found in old age, and complicating cardiovascular hypertrophy. It is also found in severe anæmia.

(b) *Calcification associated with fatty degeneration.* This condition (Fig. 11.1) first described by Mönckeberg (1903) and often described as *Mönckeberg's sclerosis*, is found particularly in the arteries of the lower extremities, where the hard medial plaques give the appearance and feel of "pipe stem" arteries or "goose's trachea." The lesions often start in foci in the centre of the media, where the calcification is surrounded by fatty degeneration; the calcification has a special affinity for elastic fibres. A most instructive account of this lesion has been given by Abrahams (1950) in a report on himself. At the age of 40 he broke a metatarsal bone running, and an X-ray showed calcification of the arteries of the foot. Twenty-five years later, having continued to run daily, and in the total absence of ischæmic symptoms, X-ray pictures showed gross calcification in all the arteries of the lower limb, from the femoral to the phalangeal artery of the great toe, but no calcification was visible in the aorta or the arteries of the upper limb. Biopsy of the dorsalis pedis showed calcification of the Mönckeberg type, and intimal thickening; biopsy of the radial showed no abnormality. The serum calcium, phosphate and cholesterol were respectively, 10.4, 3.8 and 168 mg. per 100 ml. His arterial pressure (subsequently taken by me) was 168/88. Mönckeberg's sclerosis would seem not to produce arterial occlusion.

Mönckeberg's sclerosis itself is rare in the aorta; but an essentially similar, but more diffuse and less intense, calcification is common, particularly in the abdominal aorta.

(c) *Mucous degeneration*, in which elastic lamellæ of the aorta may become separated by lozenge-shaped areas deeply stained by mucicarmine. Swollen muscle cells lie in the mucous matrix in some of these areas, but are absent in others. Turnbull describes this as rarer than the two foregoing, often associated with them, and most frequently but not exclusively, in association with cardiovascular hypertrophy.

(d) *Medial fibrosis*, an end result or accompaniment of the degenerations described above, affecting the aorta and large arteries. Medial fibrosis also occurs in the small arteries and arterioles, e.g. of the retina, brain and kidney in association with intimal proliferation and hyalinization. It was an essential component of Gull and Sutton's "arterio-capillary fibrosis."

Bell and Clawson (1928) distinguish only two medial degenerations, *calcification* and *senile ectasia*. By calcification, they refer particularly to Mönckeberg's sclerosis affecting predominantly the large arteries of the lower limbs. By senile ectasia they signify an affection of the aorta and large arteries of the elastic type in which the elastic tissue

degenerates, with numerous ruptures of the lamellæ, resulting in dilatation and thinning of the wall, and loss of elasticity.

These medial degenerations occur with advancing age and may be more common in subjects with high pressure, though there are few controlled studies. They are not found in experimental animals with hypertension due to renal artery constriction.

Medial calcification can be produced in rabbits by administration of large doses of calciferol. In dogs, calciferol in large doses may produce hypertension and arteriolar necrosis in the kidney (Goormaghtigh and Handovsky, 1938).

Medial degenerations are chiefly important in so far as they are associated with aneurysmal expansions of the aorta, particularly

aneurysms, raised arterial pressure may be an important contributory cause, for obvious mechanical reasons. Medial degenerations are probably chiefly responsible for loss of elasticity of the aorta and its large branches and thus for the systolic hypertension that occurs in some ageing people without other obvious cause (see p. 128). Often these degenerations are symptomless and remain so throughout life unless disaster has occurred. Increased pulse pressure, and tortuosity and movement of temporals and brachials are the chief signs. Calcification may be visible radiologically. Discrete plaques are most probably atheromatous; more continuous calcification of the arteries suggests medial calcification.

Infiltration of the Media

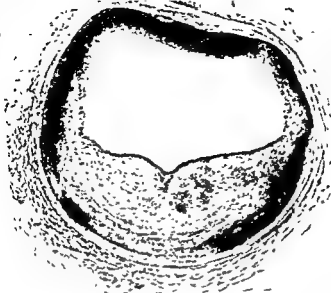
Infiltration of the media by amyloid scarcely concerns us here

THE SCOPE OF THIS BOOK.

Affections of the Intima

"Elastosis"

Elastosis, or elastic intimal thickening (Fig. 11.2), may produce a considerable increase in the thickness of the intima, largely due to newly formed layers of elastic tissue, but also to cellular intimal thickening. It occurs chiefly in the small muscular arteries, especially in the arcuate and interlobular arteries of the kidney, where the reduction in lumen may be so extreme as to produce ischaemic necrosis, with subsequent atrophy and scar formation in the territories supplied.



FIG

Note the gross concentric
connective tissue
surrounding black in
a)

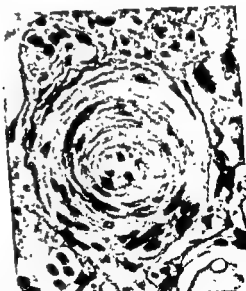


FIG 11 4 ($\times 40$) Rabbit Atheroma of aorta produced by cholesterol feeding. Two contiguous cushions of atheroma are shown. Note the gross deposit of lipid (appearing black) throughout the intima, but especially in the deeper layers. Sudan III (Dr. R. H. Heptinstall).

FIG 11 5 ($\times 500$) Regenerative intimal thickening (endarteritis obliterans) in a renal arteriole in chronic pyelonephritis. Hematoxylin and van Gieson's stain

This is the anatomical basis of the coarsely scarred or arteriosclerotic kidney. It occurs with lesser frequency in vessels of pancreas, suprarenal and brain, being rare in the arterioles of skeletal muscle, heart muscle, gut and skin. It is quite common in the digital arteries (Lewis, 1938). Elastosis occurs with increasing frequency with advancing age, and is commoner in those with hypertension than in those without. It is usually uncommon in the pulmonary arteries, but is often found there when the pulmonary artery pressure is raised as a consequence of mitral stenosis (Turnbull, 1915). This is strong evidence that it is at least in part a consequence of hypertension.

Atheroma

Atheroma (Fig. 11.3) is one of the most important lesions of the arteries, and is the chief condition which is ordinarily included in the term arteriosclerosis.

"Atheroma is a degeneration which affects, and is almost confined to, the intima. It is found in both the elastic and the muscular arteries, but is commoner in the large elastic. The degeneration is characterized by the accumulation of debris, which is at first fatty and is later frequently impregnated by calcium" (Turnbull, 1915). The chief constituent of this fatty material has been shown to be cholesterol and its esters. The Greek word *ἀθήρωμα* which is derived from *ἀθήρη*, gruel or porridge, was used by Galen to signify a tumour full of gruel-like material, which thus defines the position precisely.

Atheroma is not infrequently associated with degenerative changes in the media, and this association is sometimes given the name "atherosclerosis." Its occurrence as intimal tumours has also led to the name "nodular arteriosclerosis." Atheromatous deposits occur particularly in the aorta, especially in the arch and around the mouths of the arterial branches. When it is severe, the changes are most intense in the abdominal aorta, where the endothelium may give way, and the nodules discharge their contents to form atheromatous ulcers. Atheroma extends into the larger branches of the aorta, but is highly variable in its distribution. It commonly extends into the coronary arteries, the left being more affected than the right. The carotids are often involved, as are the vertebrals, basilar, the constituent arteries of the circle of Willis and their main branches. The arteries of the upper limb are rarely severely involved. The renals are often involved. The arteries of the lower limb are commonly severely affected, the involvement decreasing after the bifurcation of the popliteal into its anterior and posterior tibial branches.

Atheromatous nodules are of great importance since they narrow the arterial lumen, a process often suddenly completed by thrombosis. It is thus the lesion that commonly underlies myocardial infarction and

angina pectoris, cerebral thrombosis and arteriosclerotic dementia, intermittent claudication and gangrene of the senile and diabetic types.

The incidence and severity of atheroma increases with increasing age. In the older age groups in Western Europe and North America, atheroma may range from very slight to very severe. This, and its frequent association with medial degeneration, is the basis of Cazale's aphorism "On a l'âge de ses artères."

Intimal Fibrosis

"This is merely a modification of atheroma. The muscular and the elastic fibres gradually disappear and the intima becomes occupied by a dense fibrous tissue," (Turnbull, 1915).

Regenerative Intimal Thickening

Regenerative intimal thickening occurs as a result of disuse, e.g. after ligation of a vessel or in an artery supplying an area of atrophy, e.g. in the kidney in glomerulonephritis and pyelonephritis (Bell and Clawson, 1928). A similar cellular proliferation of the intima, unassociated with elastic hypertrophy in small arteries and arterioles, is described by Volhard (1931), Fahr (1922) and Fishberg (1927) as endarteritis obliterans (Fig. 11.5).

The Pathogenesis of Atheroma

The intimal deposits of lipoids, the cushions of intimal fibrosis, and associated changes in the media that are frequent, though unessential, concomitants of true atheroma, constitute atherosclerosis (Marchand, 1904), the most important of many varieties of arterial lesion found in man. The pathogenesis of these changes is now a very popular subject for investigation and here only a brief outline of some aspects of the problem will be attempted. For fuller accounts and literature, the reader is referred to Katz and Stamler (1953), Page (1954), and Gofman and others (1954).

At the present time there are two chief hypotheses which purport to explain atheroma. The first is that the intimal plaques represent a reaction, in which lipid infiltration is an important constituent, to a primary change in the arterial wall. To Virchow, the change was a necrobiosis, to Wintermütz an intramural hæmorrhage, and to Rokitsansky and to Duguid (1954) a mural thrombus. The second hypothesis is that atheroma represents the local effects of a generalized disturbance of lipid metabolism (Anitschkow, 1933; Leary, 1941). It is quite possible that these two hypotheses both contain an element of truth, and that the lesions which we classify as atheroma have more than one component.

The evidence for the first view is briefly as follows (Duguid, 1954).

subdivisions, which were, in order of frequency, apoplexy, arteriosclerosis, chronic myocarditis, chronic endocarditis and chronic nephritis. The wartime period was, of course, associated with a number of changes, one of which was a shortage of calories, particularly those derived from fat. They were, however, unable to establish a consistent difference between country, in which there was very little shortage of fats, and town, where there was extreme shortage; though they could not conclude that such a difference did not exist. Hims-worth (1949) has also pointed out that a decline in the mortality from diabetes in England and Wales coincided with food shortage induced by the German blockade in World War I, and with the introduction of rationing in World War II; this decline affected almost exclusively subjects dying over the age of 45, in which the chief causes of death are cardiovascular. In England in World War II, there was little or no shortage of calories, but both protein and fats were greatly reduced. Fullerton and others (1953) have shown that ingestion of fat may also increase the liability to thrombosis.

(v) There are certain human diseases, namely, familial xanthomatosis, diabetes mellitus, hypothyroidism, and the nephrotic syndrome (chiefly type II Nephritis) in which the blood cholesterol becomes raised. Atheroma is said to be unusually frequent in such conditions.

(vi) Blood cholesterol rises with age. At a given age the values for blood cholesterol tend to be higher in patients with coronary thrombosis than in control patients of the same age and sex.

(vii) According to Gofman and others (1950, 1952), there is a particularly close association, both in man and experimental animals, between atherosclerosis and a macromolecular lipo-protein complex having Sf values of 10 to 20 units,¹ and molecular weights of about 3,000,000.

(viii) Lesions closely resembling human atheroma can be produced in rabbit, chick and thyroid deficient dog by feeding diets rich in cholesterol (Fig 11.4). As Anitschkow first showed in the rabbit, if a relatively small dietary excess is continued for a long time, arterial lesions occur in the absence of diffuse organ lipoidosis, which is a conspicuous feature when large doses are used for short periods. However, as has been noted, experimental atheroma is not associated with thrombotic arterial lesions.

In the experimental atheroma some extent reversibility is observed if, cholesterol be removed from the diet. The degree of atheroma produced by a given dietary cholesterol is diminished by simultaneous administration of thyroid extract, oestra-

¹ These Sf values are Svedberg units of flotation, and refer to the rate at which the particles rise to the surface when centrifuged in solutions of known specific gravity.

In the first place, the most important clinical consequences of atheroma in man are the thrombotic occlusions of coronary and cerebral arteries. But, in experimental atheroma, produced by cholesterol feeding, thrombotic lesions do not occur. On the other hand, when arteries are closed, or partly closed, by emboli or mural thrombi, those thrombi become organized and infiltrated with lipoid and the lumen, if originally obliterated, becomes recanalized. Mural thrombi become covered by vascular endothelium and the underlying thrombus organizes and becomes infiltrated. The lesions present both lipoid infiltration of the intima and intimal fibrosis, the two essential components of human atherosclerosis. On this view, the atheroma which kills is essentially a thrombotic disease, mural thrombi being deposited, organized and infiltrated with lipoids playing a secondary and subsidiary rôle. According to this hypothesis, lipoid metabolism is important only so far as it may be concerned in the production of thrombi, and in determining the constituents of the tissue which remains after they have been organized.

The second view, that atheroma is metabolic in origin, is much more popular hypothesis to-day, though Duguid's objection stands, namely, that the experimental lesions are not productive of thrombotic vascular occlusion. The chief evidence in its favour is as follows (see literature see Katz and Stamler, 1954).

(i) The cholesterol content of atheromatous aortas and coronary arteries is very greatly higher than of normal aortas and coronary arteries.

(ii) Wilens (1947) found advanced atheroma of the aorta and coronary arteries was about twice as common in 305 obese persons as in 483 poorly nourished persons coming to routine autopsy at Bellevue Hospital, New York.

(iii) Atheroma seems to be commoner in those races which have a high content of dietary fat, such as the inhabitants of the United States, Great Britain and Scandinavia, than in those with a lower content of fat, such as certain sections of the Italian people, Chinese, Africans, etc. Moreover, in a particular country, the mortality from coronary artery disease seems to be higher, the higher the income group. Thus in Great Britain, the standardized mortality from coronary artery occlusion was 368 among physicians and surgeons as compared with 40 among miners, quarrymen and agricultural labourers (Ryle and Russell, 1954; Arnott, 1954).

(iv) The incidence of atheroma and deaths from it are said to decrease during times when food is short. Strom and Jensen (1945) showed that mortality from diseases of the circulatory system was rising in Norway until the outbreak of World War II; it then declined sharply until the end of the war in 1945, after which it began to rise again.

and public officials, and that the rate in these latter groups was the same as a miscellaneous non-medical group of similar age. The reason for this very high incidence in general practitioners is quite unknown. It may be used as an argument that the "pressure" of living is an important etiological factor. However, this idea has never been sufficiently precisely formulated and is hard to correlate with the reduced incidence during the German occupation of Norway.

Finally, Morris and his colleagues (1953) have shown that comparing bus conductors and drivers, telephonists, telephone operators and postmen, deaths from coronary disease are higher in the sedentary than in the active workers, though angina pectoris is rather more frequent in the latter. They suggest, therefore, that "men in physically active jobs have a lower incidence of coronary heart-disease in middle age than have men in physically inactive jobs. More important, the disease is not so severe in physically active workers, tending to present first in them as angina pectoris and other relatively benign forms, and to have a smaller early case-fatality and a lower early mortality-rate."

The Relationship of Atheroma to Hypertension

It is the general experience of pathologists that atheroma is more widespread and severe in the presence of hypertension than in its absence. Evans (1922) found it in the aorta and larger branches in three out of four children aged 14 or less who died of chronic nephritis with gross hypertension. Wilens (1947) found that for any decade and any degree of obesity, atheroma was more common in those with hypertension than in those without. The most cogent evidence that any tendency to atheroma is exaggerated by hypertension is the frequency of atheroma of the pulmonary arteries in mitral stenosis (Turnbull, 1915). The relationship between coronary atheroma and hypertension has been intensively studied by Davis and Klainer (1940a, b) who showed that marked atheroma is commoner in those with essential hypertension than in those with normal pressures, this being particularly true between the ages of 30 and 60. On the other hand, within the series with hypertension, there seemed to be no relationship between the incidence of severe coronary disease and the degree of hypertension, severe coronary disease occurred in 41.3 per cent. of hearts under 450 g. and in 41.3 per cent. of hearts over 550 g. Furthermore, they found that the incidence of severe coronary disease was the same in 46 patients who had died of renal disease (chronic and subacute nephritis in 33) as in 270 controls of similar age without hypertension. They therefore concluded that atheroma and hypertension were not causally related directly, but that both might be due to the same cause, and that perhaps atheroma, affecting

diol benzoate, potassium iodide (in the rabbit but not in the chick), but not by lipotropic factors such as choline and lipocaic.

There are, however, a number of facts that are not entirely accounted for by the lipid hypothesis. Anatomically, the lesions produced by cholesterol feeding in the rabbit are often much more extensively permeated with lipid than the lesions in man (cf. Figs 11.3 and 11.4). While Anitschkow (1933) showed that when cholesterol feeding is stopped, the deposits tend to be covered with a cellular layer, Moon and Rinehart (1952) found that the early changes in human coronary disease were fibroblastic proliferation, increase in the mucous ground substance and in degeneration of elastic tissue. They considered that the lack of correlation between lipid and early arteriosclerotic changes suggested that deposition of lipid was not the initiating factor in arteriosclerosis.

There is a good deal of evidence that the incidence of angina pectoris and myocardial infarction has steadily increased in recent years. Morris (1951) pointed out that in England and Wales the standardized death rate from coronary artery disease almost doubled between 1938 and 1948. This rise was particularly due to a rise in male death rates, those for females remaining almost stationary, so that for 1946-48 the ratio for males was almost thrice that for females. This difference in sex incidence has not been explained. As will be seen in the next chapter, hypertension is more closely related to coronary disease in the female than in the male. In order to discover the extent to which coronary atheroma had increased Morris examined the incidence of advanced coronary atheroma, taking calcification as his criterion, in 6,000 autopsies at the London Hospital, from 1907 to 1949 inclusive. While the incidence of cases of coronary heart disease increased sevenfold over this period, the incidence of coronary calcification actually decreased in all the sex, age and pathological sub-groups (including hypertensive) studied. Although studies, such as this, made on material not collected to answer the question asked, have often proved misleading in the past, this study serves particularly to prevent us from forgetting the importance of the thrombotic component.

Morris, Heady and Barley (1952) have studied the incidence of coronary disease in British doctors from the records of their Assurance Society. The incidence rose with age from a negligible figure under 40, to 12 per 1,000 age 55-59, and 17 per 1,000 aged 60-64. They estimated the probability that the individual practitioner under 45 years of age will have an attack of coronary heart disease before the age of 65 to be one in five. They found that the incidence of first attacks of coronary disease was about twice as high among full-time general practitioners as in other doctors, including full-time specialists,

Arteriolosclerosis

Bell and Clawson (1928) define arterioles as small precapillary vessels containing muscle and endothelium. In the kidney they include only the afferent and efferent glomerular arterioles. In such vessels, in association with prolonged hypertension, a deposit of hyaline material forms between the endothelium and the muscular layer; in some cases this may contain fat droplets. This fatty hyaline intimal change was clearly described by Jores (1904) and by numerous pathologists subsequently, particularly in the kidney (Fig. 11.6), but also in other organs. The *diffuse hyperplastic sclerosis* of Evans (1921) combines elastosis of the small arteries with fatty hyaline thickening of the arterioles.

The incidence and distribution of arteriolosclerosis in subjects with high blood pressure has been extensively studied by many workers, who are in general agreement. The kidney is most extensively and frequently involved, as noted by Jores (1904), Volhard and Fahr (1914), Loehlein (1917), Evans (1921) and others. Fishberg (1925) found the arterioles affected in all of 72 cases of essential hypertension; in 10 the renal were the only arterioles affected. In a subsequent paper (1927) he rejected renal arteriolosclerosis as the cause of essential hypertension, having found two cases in which the lesions were minimal, a male aged 52, with a pressure of 275/165, who died of coronary thrombosis, and a female of 58, arterial pressure 202/128, who died of cerebral hæmorrhage. Bell and Clawson (1928) found "no instances of definite sclerosis of the afferent glomerular arterioles in which hypertension could be excluded with certainty", conversely they found the changes in 90 per cent of patients with hypertension. Bell (1931) later found that the arteriolosclerosis does occur in subjects with advancing age who have not hypertension, being rare before 40 and increasing from 7.7 per cent in the fifth to 29.1 per cent. after the eighth decade; in these subjects it was never found without intimal thickening of the small arteries. It was of course, much more frequent in patients with hypertension. In renal biopsies from patients with essential hypertension, Smithwick and Castleman (1951) found arteriolar changes ranging from moderate to severe in 53 per cent., but in only 25 per cent. of patients having intermittent hypertension. The relationship between the intensity of the renal vascular changes and the arterial pressure and mortality over five to nine years are shown in Tables 11.1 and 11.2. Arteriolosclerosis and the associated elastosis of the small renal arteries may so reduce the arterial lumen that the renal tissue may atrophy. The ischæmic areas are small and numerous, producing the red granular kidney of the nineteenth century, or the "einfache blande Sklerose" of Volhard and Fahr (1914). As Fahr pointed out, arteriolosclerosis of the renal vessels is often associated with atrophy

the blood flow to a particular territory, might be the cause of hypertension.

The relationship of cerebral arteriosclerosis to hypertension has been much less adequately studied. Clinical impressions (not always trustworthy) suggest that cerebral vascular disease is much more closely related to hypertension than is coronary disease.

Moss and his colleagues (1951) have found that in the myxædematous dog, fed cholesterol, the severity of the atheroma is greater in dogs with co-existing hypertension produced by renal artery constriction. Moses (1954) observed the same in dogs in which hypertension was produced by injecting silica into the renal artery. Bronte-Stewart and Heptinstall (1954) showed that, in rabbits fed with cholesterol, hypertension produced by renal artery constriction increased the extent and severity of aortic atheroma. It is of great interest that within the series with hypertension they were unable to demonstrate any relationship between the height of the blood pressure and the degree of atheroma; their results in this respect corresponding to those of Davis and Klainer (1940a) in man.

Comment. It would seem probable, therefore, that genetic and environmental factors are concerned in the pathogenesis of atheroma. Sex, diet, blood pressure and conditions of work are all known factors. So far as diet is concerned, attention has become focused chiefly on fats and lipoids, and particularly cholesterol. Cholesterol is broken down and synthesized in the body. The blood cholesterol is not much influenced by the cholesterol content of the diet but is raised by a diet containing a high proportion of fat or a caloric intake much in excess of requirement. I would suggest that one of the best ways of finding out the rôle of dietary factors is to conduct a controlled therapeutic trial of low fat and low caloric diets in patients known to have atheromatous disease, to find out whether such diets prevent the recurrence of thrombotic episodes.

LESIONS AFFECTING SMALL ARTERIES AND ARTERIOLES

The small arteries and arterioles are, as has been mentioned, part of the same functional unit as the muscular arteries and share many of the lesions named in the last section, particularly hypertrophy of the media, fibrosis of the media, elastosis and proliferative thickening of the intima. In addition, two changes that are particularly closely related to hypertension occur only in the small arteries and arterioles, first the fatty hyaline intimal thickening known as arteriolosclerosis, which is the characteristic lesion of the benign phase and, second, the acute fibrinoid arteriolar necroses which are at once the characteristic feature, and anatomical basis, of that disastrous complication of hypertension, the malignant phase.

Fishberg concluded from the similarity between the lesions of chronic nephritic and essential hypertension that arteriolesclerosis was

arterioles has, however, never been produced experimentally and the case remains, to this extent, weak. An alternative view has been supported with great distinction. Fahr (1922) rejects this explanation because of the very patchy distribution of the lesion, its predilection for the kidney and its notable infrequency in heart, gut, muscle and skin, which are also exposed to the raised arterial pressure; he also finds it difficult to explain why raised arterial pressure should give renal lesions, sometimes of the benign, and sometimes of the malignant form. He concluded that renal vascular lesions were primary and due to toxins, and suggested that the hypertension was due to a reflex from the kidney. This explanation was supported by Hering (1930), who thought the arterial lesions were due to a poison, and that the vascular lesions produced reflex rises of arterial pressure, the reflexes originating from the territories whose vessels were narrowed.

Goldblatt's demonstration that renal artery constriction produced hypertension evoked new interest in this hypothesis. a modification

Strong (1937), who examined the organs from 100 cases with hypertension and 100 cases without hypertension. They found that the incidence of arteriolar lesions was greater in organs of subjects with high, than in subjects with normal, pressures, but that the order of frequency of involvement of the different organs was the same in the two series with the same

many workers in this field do not support this hypothesis at the present day because the lesions may be absent or minimal in the hypertension, and because it is not the widespread lesions in chronic nephritis other than as the effects of hypertension.

Fibrinoid Necrosis of small Arteries and Arterioles

In 1919 Fahr described two types of acute lesion, affecting small arteries and arterioles, which were invariably present in the condition termed by him malignant nephrosclerosis. The first type of lesion was an acute necrosis of the vessel wall with fragmentation of nuclei, deposition of fibrinoid material and the occasional presence of red blood corpuscles in the wall; the second, a cellular thickening of the intima without splitting or reduplication of the elastica interna. There

TABLE 11.1. *The Relation between the Severity of Hypertension, as gauged by the Diastolic Blood Pressure, and Renal Vascular Disease (Smithwick and Castleman, 1951).*

Severity of Hypertension	Percentage having Renal Vascular Disease	
	None to Mild	Moderate to Severe
Intermittent	75	25
Persistent :		
Diastolic blood pressure 90-109 mm. .	61	39
Diastolic blood pressure 110-139 mm.	37	63
Diastolic blood pressure 140+ . . .	29	71

TABLE 11.2. *The Mortality Rates for the various Degrees of Arteriosclerosis found in Renal Biopsies (Smithwick and Castleman, 1951)*

Degree of Arteriosclerosis	No. of Cases	Percentage Mortality 5-9 years
None	20	5
1	85	19
2	129	18
3	244	30
4	43	54

Degree 1 represents the least, 4 the most severe change.

of the media ; in other tissues the media of the affected vessels tends to be hypertrophied.

Splenic arterioles commonly show hyaline thickening in normal subjects, and Evans (1921) would only accept manifest fatty change as abnormal. In Fishberg's (1925) cases of essential hypertension, arteriolar changes were found in the spleen in two-thirds, the pancreas in one-half, the brain in one-fifth ; lesions were present in the myocardium in two of 68 cases, not at all in skin or skeletal muscle (examined respectively in 17 and 15 cases), and very rarely in gastrointestinal tract, thyroid and lungs. Fishberg (1927) found the same lesions with the same distribution in chronic nephritis, lesions being found in kidney, spleen and pancreas frequently ; in brain, liver and suprarenals less frequently ; in heart and lungs occasionally ; but in gut, skin and voluntary muscle, examined in a few cases only, no prominent lesions were found. Very similar results have been described by Jores (1904), Volhard and Fahr (1914), Fahr (1922), Evans (1921) and Bell and Clawson (1928).

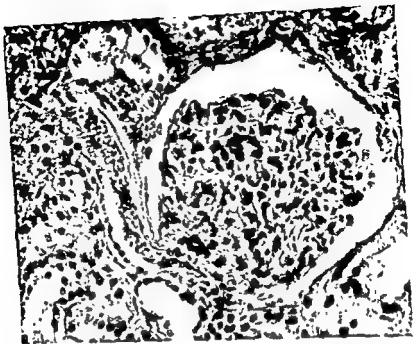


FIG. 11 6 Arteriosclerosis Fatty hyaline intimal thickening (in this case nearly all hyaline) of afferent arteriole of glomerulus (Dr. E. T. Bell).

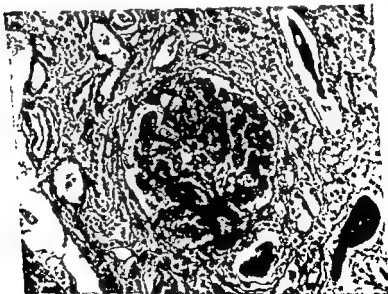


FIG. 11 7 ($\times 175$) Fibrinous necrosis of afferent glomerular arteriole and of the vessels of the glomerular tuft in the malignant phase of essential hypertension (Dr. Heptinstall)

is now general agreement that the acute fibrinoid necrosis is the anatomical basis of *malignant hypertension*. The essential feature of the acute fibrinoid necrosis is a deposition, usually in the media, but sometimes in intima, and sometimes in both, of a material which, in the fixed tissue stained with hæmatoxylin and eosin, appears bright pink and granular.

The accumulation of this fibrinoid substance, in which red cells are occasionally entangled, is accompanied by a disappearance of the muscle fibres of the media, and is sometimes associated with a mild inflammatory reaction around the vessel; this inflammatory reaction is never so severe as in *polyarteritis nodosa* (Chapter 19). It is an important issue, as yet unsettled, whether this fibrinoid change represents a simple destruction or autolysis of the constituents of the vessel wall, or an infiltration by the protein constituents of plasma. However this may be, the fibrinoid necrosis produces an expansion of the vessel wall with a gross reduction, and sometimes complete obliteration, of lumen (Figs. 11.7, 11.8, 11.9). Occurring in the afferent glomerular arteriole, it is associated with an acute necrosis of the glomerulus (Fig. 11.7). These acute necroses are usually associated with regenerative intimal thickening of small arteries and arterioles, in which the intima is grossly thickened by a cellular mass which may contain collagen fibres, but does not usually contain elastic fibres (Fig. 11.5). This "endarteritis" may represent the involution of an arteriole nearly occluded proximally or distally, or the organization of an acute necrosis. Other arterial lesions, elastosis, hyaline fatty intimal thickening, are present in varying degree.

These acute arterial lesions of malignant sclerosis lead, of course, to a progressive destruction of nephrons, and are the anatomical basis of the rapidly progressive renal failure that characterizes the malignant phase of hypertension. In some instances, where the course of the disease has been rapid, the kidney is not reduced in size, but shows a mottled red and yellow appearance of the cortex. In other instances, where the course has been prolonged, the kidney may be a little reduced in size and finely scarred, the engrafting of the changes of malignant on those of benign sclerosis.

Acute arteriolar changes are nearly always most severe and widespread in the kidney, but they occur in order of diminishing frequency in the pancreas (Fig. 11.8), adrenal (Fig. 11.9), gut, brain, eye, heart and liver but not in skeletal muscle or skin. In the gut they may be associated with minute hæmorrhagic necroses; in the brain possibly with minute infarcts and perhaps cerebral hæmorrhage; in the eye they may be associated with hypertensive neuroretinopathy, though it is not clear how the two changes are related. In the other organs they seem to be symptomless.

Acute arteriolar necroses are not confined to the malignant phase of essential hypertension. They occur in other types of severe hypertension which follow a similar clinical course and which may also be described as in the malignant phase. Loehlein (1917) described them in subacute nephritis, Fishberg (1927), Klemperer and Otani (1931), Derow and Altschule (1935), in chronic nephritis. MacMahon, Close and Hass (1934), and later Ellis (1938) described them in Cushing's syndrome. They have also been described in chronic pyelonephritis (Weiss and Parker, 1939; Pickering and Heptinstall, 1953), in pregnancy toxæmia (Klemperer and Otani, 1931), in one case of pheochromocytoma (Platt and Davson, 1950), and in one case of polycystic kidney (Heptinstall, 1953).

The pathogenesis of these acute arteriolar lesions is one of the most important problems in hypertension, since they are the basis of the most dangerous phase of hypertensive disease. Fahr (1919), who first emphasized that these lesions were primary, articular rheumatism, could produce in one case the arteriolar lesions of benign, in another the arteriolar lesions of malignant hypertension. He wrote (1922) "dass zwischen den Gefässveränderungen der benignen und malignen Hypertonie ein Zusammenhang besteht."

It was later suggested that the stimulus, hypertension, could produce in one case the arteriolar lesions of benign, in another the arteriolar lesions of malignant hypertension. He wrote (1922) "dass zwischen den Gefässveränderungen der benignen und malignen Hypertonie ein Zusammenhang besteht." This hypothesis in the malignant phase was due to release of a vasoconstrictor substance from the kidney due to arterial spasm, that the arteriolar lesions were another consequence of this vascular spasm, and that they themselves accentuated renal ischæmia leading to further ischæmia, further release of pressor substance and so to a vicious circle which was characteristic of the malignant phase.

The idea that acute necroses were due to an arterial pressure that had exceeded a certain critical value was first suggested by Wilson and Pickering as a result of experiments on rabbits and has been subsequently developed by Pickering (1942, 1952b). The speed with which the rise of blood pressure occurs also seems to be an important factor. In terms of this hypothesis, Fahr's dilemma is resolved by the type of arteriolar lesion being chiefly related to the degree of hypertension, and the speed with which it is attained. The experimental evidence for this hypothesis has already been fully discussed in Chapter 5. The hypothesis is clearly compatible with the pathological evidence since it explains the appearance of these necroses in a great variety of types of disease associated with severe hypertension. The clinical evidence will be more fully discussed in Chapter 13. Here it may be said that the bulk of the clinical evidence is in favour. Thus

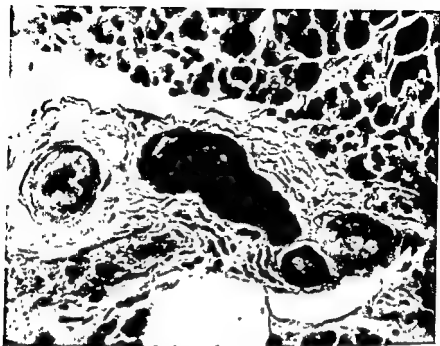


FIG 11 8 ($\times 350$) Fibrinoid necrosis of small artery of pancreas The lumen is nearly obliterated (Dr. Heptinstall)

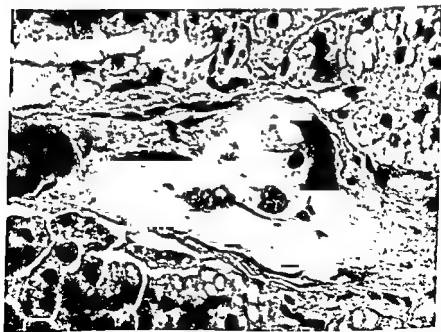


FIG 11 9 ($\times 550$) Fibrinoid necrosis of arteriole of adrenal in malignant hypertension The lumen is nearly obliterated (Dr. Heptinstall)

This explanation is further supported by the occurrence in mitral stenosis of acute arteriolar necroses of the pulmonary arteries (Parker and Weiss, 1936; Hicks, 1953); in these cases the right ventricle was hypertrophied and the pulmonary artery pressure presumably greatly raised.

Nevertheless, there are exceptional cases in which the hypothesis does not appear to fit. Thus one of Fishberg's (1927) cases of nephritis, in which acute necroses were found, is said to have had a normal arterial pressure, though it is possible that the arterial pressure was raised before she came under observation in the terminal phase. More difficult is Perera's (1954) patient in whom neuroretinitis developed during a phase of lowered arterial pressure following a myocardial

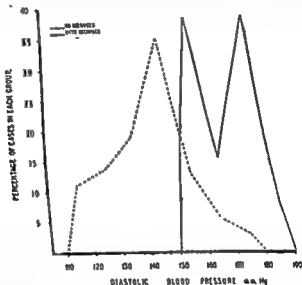


FIG 11.11 Shows the incidence of various diastolic pressures in patients whose renal biopsies showed the absence or presence of arteriolar necroses. The blood pressures were the average values before operation. There are clearly two populations with some overlap (Heptinstall (1951), *Brit. Heart J.*, 16, 133).

infarction and who died of uræmia with arteriolar necroses in the kidneys post-mortem. For the present this exceptional type of case remains quite unexplained.

It is, however, to be noted that acute arteriolar necroses are not restricted to malignant hypertension. They may occur in the edges of infarcts, in areas of intense vasoconstriction produced by pituitrin, in inflammatory lesions, and in the so-called collagen diseases, particularly polyarteritis nodosa (Chapter 19). The histological change is no doubt the end result of a number of different processes. In the

it has been the general experience of physicians, since Volhard, that malignant hypertension is found in those patients with arterial pressures in the higher ranges. Recently Heptinstall (1954) has compared the types of arterial lesion found in renal biopsies, taken at operation for sympathectomy, with the blood pressures recorded before operation. Fig. 11.10 relates the degree of change in the small arteries and arterioles to the arterial pressure. The relationship is clear. As the arterial pressure rises, the severer grades of change appear for the first time and increase in frequency. This is particularly notable for the arteriolar necroses which begin to appear with a diastolic of 150

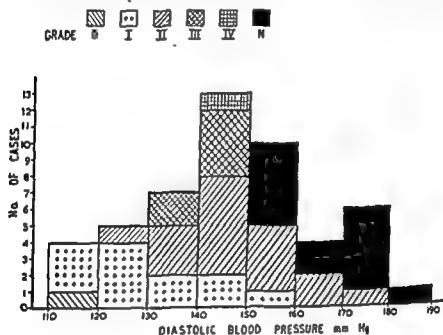


FIG. 11.10. Shows the relationship of the grade of change in the small pressure in
 biopsies were
 " is graded
 (54), *Brit.*
Heart J., 16, 133f.

and become more frequent as the pressure rises. Fig. 11.11 shows the frequency distributions of the diastolic pressures in those patients (a) in whom arteriolar necroses were present in the biopsy, (b) in whom arteriolar necroses were absent. These seem to be different distribution curves, though they overlap. These figures provide convincing evidence for the view that arteriolar necroses in human malignant hypertension are a consequence of the level of arterial pressure, a hypothesis which is further supported by the demonstration that the malignant phase may be reversed to the benign if the pressure is lowered (Pickering, Wright and Heptinstall, 1952).

CHAPTER 12

ESSENTIAL HYPERTENSION. CONCEPT AND CLINICAL FEATURES

THE CONCEPT OF ESSENTIAL HYPERTENSION

In previous chapters we have traced the development of methods of measuring arterial pressure ; the recognition of a group of diseases in which the arterial pressure is high ; the gradual process of isolating from this group conditions having well-defined clinical and pathological properties ; and finally, the existence, after this elimination, of a large remainder in which as yet no specific lesion has been recognized as the cause of the raised arterial pressure. It is this group, so-called essential hypertension, with which we are here concerned.

Thought and writing, scientific investigation and practical doctoring are all intimately dependent on the current concept of disease. The work described in Chapters 8 and 9 has led to a rejection of the concept now prevailing and the development of a new concept of essential hypertension more in accord with the facts than the old. It seems appropriate, therefore, briefly to contrast the old and the new concepts

THE CONCEPT NOW GENERALLY HELD

The current concept starts with the assumption that essential hypertension is a specific disease entity ; though there is some disagreement as to whether it is the arterial pressure or the vascular disease, or something else more tenuous, that is the basic abnormality. By a specific disease entity is meant that patients with essential hypertension exhibit a qualitative difference from

is one ;

that is

be wrong. The first wrong principle is that a dividing line can and should be drawn between "normal blood pressure" and "hypertension." This question was fully considered in Chapter 8 and will not be further discussed here. The principle has, however, certain implications that must be noted.

The chief implication of this principle is that essential hypertension can be divided into three stages : (1) A stage of "pre-hypertension," (2) a stage of "transient or labile hypertension," and (3) a stage of "fixed hypertension." What these three stages mean (see, for

collagen diseases, Klemperer (1954) has suggested that the fibrinoid material deposited in the connective tissue and the walls of blood vessels is derived from an abnormal plasma protein. That found in disseminated lupus gives staining reactions suggesting that it is derived from a nucleoprotein.

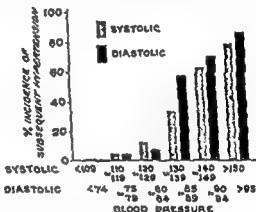
SUMMARY

Most of the arterial changes described in this chapter occur in patients whose arterial pressures are in the lower ranges, though they are more frequent and severe in those whose arterial pressures are raised. Some, particularly the medial degenerations, weaken the wall and predispose to rupture of the vessel (as in cerebral hæmorrhage, and dissecting aneurysm of the aorta). Others, especially intimal, notably atheroma of the largest arteries, elastosis of the medium arteries, and fatty hyaline intimal thickening of the smallest, narrow the lumen and produce ischæmic changes in the organs supplied, especially when, in the case of atheroma, thrombosis supervenes. All these changes increase in frequency and severity with age, and, in this sense, may be regarded as ageing processes. However, there is one change, fibrinoid arteriolar necrosis, which is the anatomical basis of malignant hypertension and which would appear to be a consequence of the hypertension itself. It is suggested that acute fibrinoid arteriolar necrosis is a consequence of the intensity of the hypertension and of the speed with which it develops, and not of the lesion which ultimately causes the raised pressure. This explanation is compatible with most of the evidence.

cardiovascular renal disease, were consistently higher in those with transient hypertension than in those without.

The conclusions which these workers have reached seem to bear out those reached in more general terms in earlier chapters, namely, (1) that arterial pressure varies from day to day and that variations are greater in some subjects than others, (2) that arterial pressure tends to rise with age and the rate of rise is greater in some subjects than others, and (3) that at any age, expectation of life is inversely related to arterial pressure. But it is rather tragic that the interpretation of data should have been so artificially restricted to their relation to the readings 160/100 and 150/90. It is still to be hoped that someone will provide the facts concerning the fluctuations of arterial pressures of individuals over the course of at least two decades without inter-

FIG. 12.2 As Fig 12.1 but related to hypertension twenty years later.



preting them through an assumption which robs them of much of their value, as well as being quite unjustified.

With the idea that the late stage of essential hypertension may follow the benign or malignant course, I have no disagreement. Current concepts of the nature of the malignant phase are, however, extremely vague, and provide little in the way of ideas that can be tested. Terms such as "accelerated vascular disease" or "vasculitis," seem to do little more than provide alternative names for the anatomical lesion which is generally agreed to form the basis of the condition.

The assumption that essential hypertension represents a

fault and in the sense of the interplay between inheritance and environment. Research inspired by such an idea has been rewarding in that much useful and basic data have been won. But the unique cause has, as yet, failed to materialize. On the functional side, overaction of the vasomotor nerves, inaction of the carotid sinus and depressor

example, Goldring and Chasis, 1944 ; Fishberg, 1954) is this. In the "pre-hypertensive" phase, the casual arterial pressure is rather high for the patient's age but has not reached the arbitrarily selected division between normal blood pressure and hypertension. In the stage of transient or labile hypertension, some casual pressures exceed the limit, others are below. In the stage of fixed hypertension, all casual pressures are above the limit. When so defined, dividing the disease into the three phases seems harmless enough. But it has unnecessarily restricted the usefulness of much careful work. It has been mentioned that one of the gaping chasms in our knowledge is of the extent to which blood pressures of different individuals increase, decrease, remain stationary, or move up and down over the course of years. Such data as have been accumulated are, unfortunately, nearly all expressed in terms of hypertension and not in actual measurements.

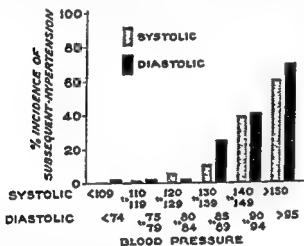


FIG. 12.1. Relationship of blood pressure to incidence of subsequent hypertension ten years later, when hypertension is defined as 160/100 or over. (Figure from Harris and others (1953), *Circulation*, 7, 874. Data from Hines (1940), *J. Amer. med. Ass.*, 115, 271).

Two may be selected as illustrative. Hines (1940) recorded the incidence of hypertension (arterial pressure 160/100 or greater on more than one reading) in 1,522 patients who had had pressures below this level at their first visit to the Mayo Clinic ten and twenty years before. Figs. 12.1 and 12.2, obtained by Harris and others (1953) from Hines' data, show that the nearer the pressure to 160/100 at the first visit, the greater the probability of hypertension ten years, and, *a fortiori*, twenty years later. Levy and others (1944) analysed the case records of 22,741 army officers who were under observation from one to more than twenty-five years. Defining hypertension as 150/90 or over, they found that :

- the frequency of transient hypertension increased with age ;
- at all ages sustained hypertension developed more frequently in those with previous transient hypertension than in those who never showed an elevated blood pressure ;
- both the rate for disability retirement, and the death rate due to

is that, at any age, the higher the arterial pressure, the less the expectation of life. This is not a qualitative difference; it is quantitative and the quantitative relationship probably operates over most, if not the whole, of the blood pressure range. There is something to be said for retaining the name to apply to the upper ranges of blood pressure, so long as we do not specify too closely what the ranges are, or suppose that the name describes anything but a rather heterogeneous group. As doctors, our chief concern is to discover why these subjects should, in a general way, have an increased mortality and why this should be related to the height of the blood pressure. This problem will be examined further in this and the next two chapters. But it may be said that one of the chief causes of the increased mortality is organic

yet too little is known about it. In the last chapter, an attempt was made to classify the different kinds of arterial disease that occur in ageing subjects and particularly in those with high blood pressure. Most of these kinds of arterial disease occur in subjects with blood pressures in the normal ranges, but several seem to occur with special frequency, or perhaps to provide a special hazard, in subjects whose blood pressures are high. The term hypertensive vascular disease would thus seem rather misleading, since it would imply a much more specific relationship of vascular disease to high blood pressure than has been demonstrated or, indeed, on the evidence, seems likely. Those vascular defects which occur with arterial pressures both in the lower (or "normal") and in the higher (or "hypertensive") ranges are on the whole stable for long periods until a vessel bursts or clots. Those patients with "essential hypertension" whose vascular lesions have this stable character are much the most numerous and are described as having benign essential hypertension or, as I prefer it, essential hypertension "in the benign phase."

There is, however, one vascular lesion that is in various

When the distribution curve for blood pressure upwards, we see, therefore, that the vascular lesions remain more or less the same in kind, though perhaps increasing in degree, until the threshold of the acute fibrinoid necrosis is reached, when this new feature, a qualitative change, intrudes. The effects of hypert

reflexes, disorder of the vasomotor centre, overproduction of adrenaline, of noradrenaline, of adrenal cortical steroids, of posterior pituitary substance, of anterior pituitary substance, of renin and of numerous other less well-authenticated substances, have been amongst the more recent claimants. From the biological standpoint, essential hypertension has recently been regarded as due to an inherited fault carried by a gene behaving as a Mendelian dominant ; as a disorder of adaptation ; as a psychosomatic disorder expressing a defect of personality, as a disease of " stress " ; and as a dietary disease due to the excessive ingestion of protein salt or some other less well defined constituent. None of these has, as we have seen, been fully substantiated.

THE NEW CONCEPT OF ESSENTIAL HYPERTENSION

In Chapters 8 and 9, were set out the considerations that led Hamilton, Roberts, Sowry and myself to the conclusion that the fundamental assumption of a qualitative difference between essential hypertension and normality was, if not wrong, at least without any substantial justification. The alternative assumption, that differences between so-called normal subjects and those with essential hypertension were quantitative, proved, as we saw, to conform more closely with the facts.

The first implication of this alternative assumption is that essential hypertension is not a specific disease entity, in the sense that typhoid fever, or even rheumatic fever are. It is the name given to a collection of subjects with high blood pressure, and in whom no specific lesion has been found to account for the high pressure. Essential hypertension, in fact, represents the right hand end of frequency distribution curves that show continuous variation (Figs. 8.2 and 8.3). There is no such thing as a dividing line between normality and hypertension. Moreover, there are degrees of hypertension. In fact, the differences are quantitative, not qualitative.

We, therefore, stop pursuing the futile search for a dividing line between normality and hypertension. We go further, we say that any such attempts are merely attempts to create artefacts, with all the confusion that ensues on the acceptance of an artefact as a real phenomenon. Again, the division of the early course of essential hypertension into stages of pre-hypertension, latent hypertension and fixed hypertension is regarded as a secondary artefact, consequent on the first ; a classification, moreover, that imperfectly describes diurnal and other variability and the effects of age noted in Chapters 2 and 8.

Finally, the doctrine of an unique cause is regarded as being probably inapplicable to essential hypertension.

So much having been swept away, what is to be substituted ? The justification for retaining the concept of essential hypertension at all

between normal blood pressure and the raised blood pressure of essential hypertension; the difference is quantitative. To make a sharp division between normal blood pressure and hypertension is quite unjustifiable, since essential hypertension represents no more than the upper end of frequency distribution curves showing continuous variation. Since the sharp division goes, so do the stages of pre-hypertension, labile hypertension and fixed hypertension.

Although normality and hypertension merge into one another and are purely relative terms, the concept of essential hypertension is retained because expectation of life has been found to be inversely related to blood pressure, the excess of deaths being largely due to vascular disease. Here again, the differences are quantitative, probably over the whole blood pressure range. With moderate elevations of arterial pressure, the chief vascular lesions are such as are also found at lower pressures; these vascular lesions have a relatively stable course and the hypertension is said to be in the benign phase. With very high pressures, there occurs a new lesion, fibrinoid arteriolar necroses, which appears to be an effect of the grossly raised pressure; the development and progress of these lesions are responsible for the rapid deterioration that characterises the malignant phase.

THE CLINICAL FEATURES OF ESSENTIAL HYPERTENSION ONSET AND EARLY COURSE

In view of what has just been said, no further reference need be made to the stages of pre-hypertension, labile hypertension and fixed hypertension. Since it is my deliberate intention to abstain from defining what constitutes an abnormal arterial pressure, it follows that the onset and early course of essential hypertension disappear, as it were, into the mist. Instead the reader is reminded that arterial pressure tends to rise with age, though the variability in course among individuals is not known. There is a suggestion from a few case records that in some subjects arterial pressure may remain stable for years; in others it may rise slowly, in a few it may rise fast; and in a few it may fall; but the frequency of these courses and the factors determining them need investigation. At any age arterial pressure tends to be higher in those whose close relatives have high pressures. There is a suggestion that the rate of rise of pressure with age depends on environmental factors, but this is not proved. Finally, he is reminded that the arterial pressure fluctuates more in some subjects than others, on the whole, a given stimulus tends to produce a larger response the higher the initial pressure.

Such are the chief generalisations that . . . concerning
the fact . . . become
namely,

occur in the course of any kind of hypertension and that it is, therefore, correct to speak of hypertension "in the malignant phase"; and that it can be reversed by reducing arterial pressure. These points are further developed in Chapter 13.

Finally, we come to the question of etiology. It seems that essential hypertension is polyphyletic in origin. It is the resultant of a number of factors that operate in greater or lesser degree in the population at large. The first factor is age. Arterial pressure tends to rise with age and the rise is greater in some subjects than others. How big these differences are will not be known until individuals have been followed for long periods and the results expressed in units other than "presence or absence of hypertension." The second is inheritance. It has now been shown that blood pressure is inherited as a graded characteristic, like height, and that the degree of resemblance is of the same order in both the lower ranges and in the higher ranges comprised by so-called essential hypertension. Inheritance, however, accounts for only a part of the variance of blood pressure observed, when allowance is made for effects of age and sex. The third group of factors is environmental. These are believed to be of the greatest importance, but, so far, the influence of the several possible factors has not been sufficiently well defined; there is, however, the suspicion (see Chapter 10) that factors operating through the mind may tend to elevate arterial pressure, while others, such as dietary deficiencies and chronic infections, may tend to lower arterial pressure.

Those three factors, age, inheritance and environment, to which we should add sex, since this slightly influences the effects of age and greatly influences prognosis (Chapter 14) are, so far as is known, the only factors concerned in the pathogenesis of essential hypertension. They are factors that affect in varying ways and degrees the whole population. We should also expect them to operate in secondary hypertension, where their effects have not yet been investigated. But in secondary hypertension we have a new factor of great potency, in raising arterial pressure, provided by the specific lesion. And so it comes about that severe hypertension in a young person is nearly always secondary.

SUMMARY

The old concept assumes that subjects with essential hypertension differ qualitatively from those with normal pressure and that a sharp line can and should be drawn between the two. It divides the early stages of hypertension into "pre-hypertension," "labile hypertension" and "fixed hypertension." It assumes that an unique cause is likely and numerous suggestions have been made as to its nature.

The new concept doubts the existence of a qualitative difference

between normal blood pressure and the raised blood pressure of essential hypertension; the difference is quantitative. To make a sharp division between normal blood pressure and hypertension is quite unjustifiable, since essential hypertension represents no more than the upper end of frequency distribution curves showing continuous variation. Since the sharp division goes, so do the stages of pre-hypertension, labile hypertension and fixed hypertension.

Although normality and hypertension merge into one another and are purely relative terms, the concept of essential hypertension is retained because expectation of life has been found to be inversely related to blood pressure, the excess of deaths being largely due to vascular disease. Here again, the differences are quantitative, probably over the whole blood pressure range. With moderate elevations of arterial pressure, the chief vascular lesions are such as are also found at lower pressures; these vascular lesions have a relatively stable course and the hypertension is said to be in the benign phase. With very high pressures, there occurs a new lesion, fibrinoid arteriolar necroses, which appears to be an effect of the grossly raised pressure; the development and progress of these lesions are responsible for the rapid deterioration that characterises the malignant phase.

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Such are the chief generalisations that may be made concerning the behaviour, over years, of arterial pressures that ultimately become high. But there is another aspect to essential hypertension, namely,

vascular disease. Here, when we are considering early stages, we are concerned only with those found in the so-called benign phase. Many of the relevant vascular lesions also occur in subjects with what current notation describes as normal pressures. Moreover, the presence and extent of those lesions can usually not be demonstrated in life unless an artery has thrombosed or ruptured. Were the course of essential hypertension described in terms of blood pressure only, then it is possible for a major vascular disaster to occur at any point of the course. In terms of current and now obsolete notation, a fatal myocardial infarction can occur in the stage of "pre-hypertension," "labile hypertension" or "fixed hypertension," though there is some evidence to suggest that coronary artery and cerebral artery lesions are differently related to arterial pressure.

AGE OF ONSET AND PRESENTING SYMPTOMS AND SIGNS

When hypertension is of gradual onset and development, as is usually the case in essential hypertension, it is usually symptomless until the arterial pressure is very high, or until a vessel is occluded or bursts. Very high pressures are themselves chiefly concerned in the production of attacks of left ventricular failure (cardiac asthma), "hypertensive neuroretinopathy," hypertensive headache, possibly cerebral hæmorrhage, and, to a lesser extent, congestive cardiac failure. The other symptoms are chiefly due to vascular disease which, indeed, probably contributes also to the symptoms just mentioned, particularly cerebral hæmorrhage. Since vascular disease is, at least in part, a consequence of advancing age, most patients with essential hypertension presenting with symptoms of the benign phase belong to the later age groups; thus in Soby's series, the peak ages of presentation were 50-54 in women and men with malignant nephrosclerosis, and 65-69 in women and 60-64 in men with benign essential hypertension.

Nevertheless, current definitions of high arterial pressure bring many subjects to the notice of their physicians before they have any symptoms properly belonging to hypertension. The age of presentation naturally varies with the frequency with which the population at large visit their doctors, the frequency with which those doctors measure blood pressure, and the levels accepted as indicating hypertension; the symptoms vary with the incidence of disease and with the kinds of complaints which take patients to doctors. Thus we find the ages and early complaints of Janeway's series, accumulated in New York in nine years up to 1913, different from those of Ayman and Pratt published in 1931 from Boston. In Ayman and Pratt's series the chief early complaints were headache in 72 per cent., pain in 67 per cent., nervousness in 67 per cent. The incidence of these symptoms was very similar to those found

in fifty psychoneurotic subjects with normal blood pressures. The high incidence of psychoneurotic symptoms in patients with hypertension may have three explanations; it may be because psychical disturbances play a part in pathogenesis; it may be that the discovery of high blood pressure induces a psychoneurosis; and it may be that patients who are discovered to have hypertension present with psychoneurotic symptoms, simply because these are much the most common symptoms which bring patients to doctors. While there may be some truth in the first, the second and third considerations are certainly true both in Great Britain and the United States to-day.

THE LATE COURSE OF ESSENTIAL HYPERTENSION; THE BENIGN AND MALIGNANT PHASES

The causes of death in patients with essential hypertension are shown in Table 12.1. Much of the variation found in this table is

TABLE 12.1. *Causes of Death in Essential Hypertension.*

Year	Author	Number of Cases	Heart Disease %	Cerebral Apoplexy %	Uremia %	Intercurrent Disease %
1913	Janeway	212	33	14	23	30
1921	Romberg	113	45	44	11	0
1923	Hunter and Rogers	2,838	33	16	16	37
1926	Christian	151	32	25	4.5	25
1928	Fahr	1	50-65	35-40	10	—
1944	Goldring and Chausse	667	66.4	14	8.5	11.1
1946	Bechgaard	293	45	16.2	10.2	29.5

due to the method of selection. The high incidence of uræmia in Janeway's series may have been due to the inclusion of cases of chronic nephritis. Probably the most representative series are those of Hunter and Rogers (1923), which shows the data of insurance candidates, and those of Bechgaard (1946) which show the general population.

The relationship between the early symptoms, with which the patient first presented, and the final mode of death is shown in Table 12.2, which emphasizes how widespread are the effects of hypertension.

Our understanding of the different courses exhibited by patients with essential hypertension is derived from the work of Volhard and Fahr (1914). They showed that essential hypertension might follow one of two courses. In most patients, the course was long with little change from year to year, and death when at last it came, was due to

vascular disease. Here, when we are considering early stages, we are concerned only with those found in the so-called benign phase. Many of the relevant vascular lesions also occur in subjects with what current notation describes as normal pressures. Moreover, the presence and extent of those lesions can usually not be demonstrated in life unless an artery has thrombosed or ruptured. Were the course of essential hypertension described in terms of blood pressure only, then it is possible for a major vascular disaster to occur at any point of the course. In terms of current and now obsolete notation, a fatal myocardial infarction can occur in the stage of "pre-hypertension," "labile hypertension" or "fixed hypertension," though there is some evidence to suggest that coronary artery and cerebral artery lesions are differently related to arterial pressure.

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1923	Hunter and Rogers	2,638	33	15	15	37
1926	Christiansen	131	32	25	4.5	23
1928	Fahr	?	50-55	35-40	10	—
1944	Golding and Chassin	867	68.4	14	8.5	11.1
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due to the method of selection. The high incidence of uræmia in Janeway's series may be due to the fact that he included cases of nephritis. Probat and Rogers (1923) found that 37% of their cases died of uræmia, those of Bechgaard 29.5%, and those of Golding and Chassin 11.1%. These figures show the causes of death in patients with essential hypertension. The high incidence of uræmia in Janeway's series may be due to the fact that he included cases of nephritis. Probat and Rogers (1923) found that 37% of their cases died of uræmia, those of Bechgaard 29.5%, and those of Golding and Chassin 11.1%. These figures show the causes of death in patients with essential hypertension.

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change from year to year, and death when at last it came, was due to

TABLE 12.2. *The Relation of Prominent Early Symptoms with High Blood Pressure to Causes of Death (Janeway, 1913 (abridged)).*

Symptoms						Causes of Death	Male		Female		Total
Dyspnea	Anginal Pain	Polynuria	Visual Disturbances	Headache Typical	Hemiplegic Attacks		No	%	No	%	
48	11	11	2	3	4	Gradual cardiac insufficiency	48	35	12	25.5	60
18	3	29	9	16	7	Coma or gradual uræmia	31	22.6	15	31.9	46
11	2	1	2	4	5	Cerebral apoplexy or its results	20	14.6	9	19.1	29
3	6	1	0	1	1	Angina pectoris	10	7.3	0	—	10
6	1	2	0	0	0	Edema of lungs	6	4.4	1	2.1	7
2	0	0	0	1	1	Progressive anæmia	1	0.7	2	4.3	3
0	0	0	0	0	0	Pericarditis	1	0.7	0	—	1
3	3	1	0	0	0	Complicating acute infectious disease	9	6.6	4	8.5	13
1	1	1	0	2	1	Other accidental causes	7	5.1	2	4.3	9
11	7	5	0	3	5	Unknown	25	—	3	—	28
3	1	1	0	1	0	Sudden	4	2.9	2	4.3	6
106	35	52	13	31	24		162		50		212

heart failure, cerebral vascular disease or intercurrent disease. These patients did not show albuminuric retinitis; nor did they develop more than a mild renal insufficiency. The kidneys, obtained after death from such patients, showed a simple bland sclerosis (einfache blande Sklerose), the arteries showing splitting of the elastica, and the arterioles a fatty hyaline change, but, apart from areas of sclerosis due to these changes, the nephrons were well preserved. In some patients, however, mostly rather younger, and with typically a higher diastolic pressure, the onset of a different course was heralded by the appearance in the fundus oculi of the changes characteristic of albuminuric retinitis; then, or soon afterwards, protein, red cells and casts appeared in the urine, renal function began rapidly to decline, and death would occur usually within a year of the onset of retinitis, from uræmia, cerebral hæmorrhage or heart failure. In these patients the kidneys after death showed not only the changes in the arteries and arterioles just described, but also severe endarteritis and changes in the renal substance resembling nephritis. This kidney they named the "Kombinationsform," because they believed that it resulted from the superimposition of an exogenous infective nephritis on an endogenous primary vascular hypertension. In 1919 Fahr described the two types of arterial lesion which were always present in this condition which he named malignant nephrosclerosis, namely, acute arteriolar necrosis, and cellular intimal thickening. Subsequent work by others, notably Keith, Wagener and

ernohan (1928), Fishberg (1939) and Ellis (1933), has fully confirmed these early clinical and pathological studies of Volhard and Fahr.

It is to be noted that the term malignant hypertension refers to a clinical diagnosis, made on the finding of hypertensive neuro-retinopathy in a patient with high blood pressure; a supporting fact being rapid deterioration in kidney function. The term malignant nephrosclerosis is, strictly speaking, a pathological diagnosis based on the histological findings in the kidney and other organs, and particularly in the presence of arteriolar necroses. Though there is no reason to doubt that both terms refer to the same set of disease processes, they are not quite synonymous, for there is not a precise correspondence in time between the onset of hypertensive neuro-retinopathy and renal arteriolar necroses (see p. 285).

It is now very generally agreed that the different courses of benign and malignant hypertension are due to the presence in the malignant, but not in the benign form, of these acute arteriolar necroses. It is the reduction in blood flow produced by the swelling of the vascular walls occasioned by these necroses that produces the rapid decline of renal function that is the outstanding clinical feature of the malignant phase. The evidence presented in Chapters 5 and 10 suggests that the chief factor producing these arteriolar necroses is a grossly raised arterial pressure, and thus leads to the hypothesis that the difference between the benign and malignant phases of hypertension is not a consequence of the kind of hypertension, but of its degree.

This hypothesis will be re-examined in the next chapter. Meanwhile, we may consider in greater detail the nature of the disturbances to which hypertension gives rise.

HYPERTENSION AND THE CENTRAL NERVOUS SYSTEM

SUBJECTIVE SYMPTOMS REFERABLE TO THE NERVOUS SYSTEM

In Bechgaard's (1946) series of 1,038 out-patients, who at first examination had a blood pressure of 160/100 or a systolic of 180 mm. Hg or above, 65 per cent. complained of no symptoms referable to the central nervous system, 18 per cent. complained of dizziness, 15 per cent. of headache, and 2.5 per cent. of the sequelae of cerebral vascular lesions. A still commoner symptom was fatigue, particularly in the higher age groups, this fatigue was often experienced particularly in the morning, was not caused by work, and lowered initiative throughout the day, in many instances it was associated with poor sleep.

Headache

Headache is one of the most frequent complaints in patients with hypertension. Ayman and Pratt (1931) concluded that as a very early

sign it was of psychoneurotic origin. Stewart (1953) came to the same conclusion. He found that of 104 patients who were unaware of their hypertension 87 had no headache, while of 96 who were aware they had hypertension only 25 had not complained of headache. He thought it was almost impossible for a patient who had been told of hypertension to remain symptom-free. Headaches are, in fact, very common in the population at large, and present a variety of types of varying aetiology, which have been reviewed elsewhere (Pickering, 1950b). Any of these may be the symptom bringing the patient to the doctor. Again, headaches are more conspicuous in those who are anxious, as are patients who have just been informed that their arterial pressure is high.

However, there is a type of headache which is almost pathognomonic of high blood pressure, which tends to be associated with gross hypertension and which has certain features suggesting an organic origin. This characteristic headache is usually occipital, but is occasionally felt elsewhere over the calvarium. It is there when the patient wakes in the morning and tends to disappear as the day wears on, often lasting an hour or so, but, when severe, lasting much longer. When severe it may be accompanied by nausea and vomiting. That this symptom is not dependent on the patient's awareness that he has hypertension is clearly shown by the following description by Bright (1836a): "It very frequently happens, when listening to the detail of symptoms, in connection with deranged cerebral function and threatened apoplexy, that we find the patient laying considerable stress upon a constant or frequently recurring pain over the occiput." This is the headache to which Janeway (1913) referred as "typical," and to which the figures in Table 12.2 refer.

I have never been able to elucidate the mechanism of this headache. Since it may also come on if the patient sleeps in the day, it seemed possible that it was related to the horizontal posture, but inducing patients to sleep alternate nights on three pillows and on one revealed no correlation. Nor have I been able to modify the pain by occluding the carotid in the neck, though this is usually effective in migraine, and often in the headaches associated with fever and following injection of histamine and lumbar puncture (Pickering, 1939). In a given patient with hypertension the c.s.f. pressure is not higher when the typical headache is present than when it is absent; but removing c.s.f. often aggravates the pain (Pickering, 1934). I have the impression that morning headache is most outstanding in subjects with severe hypertension; it is in general greatly relieved by lumbo-dorsal sympathectomy, and by the effective reduction of arterial pressure by hypotensive drugs.

Vertigo

Vertigo, occurring in attacks, or as a persistent disturbance aggravated by posture or movement is not an uncommon symptom in patients with hypertension, particularly elderly patients in the benign phase. It is probably due to organic vascular lesions in the labyrinth or its nervous connections. It may be of sudden onset, and associated with nausea and vomiting; the attack taking several days to pass off. It is then probably due to a hæmorrhage into the labyrinth or to a vascular accident involving the central connections of the labyrinth. Vertigo is an integral component of some of the complex vascular syndromes, such as that produced by thrombosis of the posterior inferior cerebellar artery.

CEREBRAL DISTURBANCES

Cerebral disturbances occurring in the course of hypertensive disease are of several kinds. The "stroke" or apoplexy, has long been familiar as a manifestation of cerebral hæmorrhage and thrombosis. In addition, transient attacks occur, which are of two very different kinds. The first type is characterized by a localized paralysis without loss of consciousness, the second by convulsions and coma, the latter clearly reflecting a more diffuse disturbance. These have in the past been grouped together as the acute and chronic pseudo-uræmia of Volhard (1931) and the hypertensive encephalopathy of Oppenheimer and Fishberg (1928). These two varieties of transient attack are almost certainly totally different in pathology, the one being a "little stroke" and having a similar pathology to the more familiar attack, the other being of more uncertain cause. Cerebral vascular disease of a more diffuse type may produce dementia not preceded by isolated attacks. Finally, uræmia itself produces cerebral symptoms.

CEREBRAL VASCULAR ACCIDENTS

Apoplexy: the Stroke

A wide range of attacks is comprised under this heading. At one end is the sudden loss of consciousness followed quickly by the phenomena of cerebral compression and death. At the other end is the isolated motor or sensory deficit, the so-called "minor stroke," which is clearly a local phenomenon, due to a small hæmorrhage or of an infarct due to vascular occlusion. There is still, therefore, a good deal of doubt as to how far it is possible to distinguish between cerebral hæmorrhage and cerebral thrombosis. The following points of distinc-

tion which seem to have been helpful to me are therefore offered with diffidence. The attack in cerebral hæmorrhage tends to show the following features : (a) headache is often conspicuous at the onset, and after the patient recovers consciousness, if he does so ; (b) consciousness is usually lost soon after the onset ; (c) more than half never recover consciousness but die in the attack ; (d) neck rigidity is sometimes striking, developing some four hours after the onset ; (e) the cerebrospinal fluid is often blood-stained ; (f) the phenomena of compression of the brain, a slow irregular pulse and Cheyne-Stokes respiration are not uncommon. Similar phenomena occur in subarachnoid hæmorrhage, from which intracerebral hæmorrhage has to be distinguished ; whereas in intracerebral hæmorrhage focal signs are those of interference with cerebral tissue, in subarachnoid hæmorrhage these signs arise largely from cranial nerves, particularly the oculomotor nerves. Conversely, cerebral thrombosis tends to show the following : (i) headache is rather uncommon, (ii) consciousness is frequently retained, though in a large lesion it is lost, (iii) more than half the patients recover from their attack, (iv) neck rigidity is absent, and (v) the c.s.f. is not blood-stained. Cerebral embolism has features precisely similar to those of cerebral thrombosis, but its onset is invariably sudden and it cannot be diagnosed in the absence of a source for the embolus. In hypertension, auricular fibrillation and myocardial infarction provide the only two such sources that are not extremely rare.

Within these general confines the clinical manifestations of cerebral thrombosis and embolism are extremely variable, depending on what part and how much of the brain has had its function suspended. For details concerning the symptoms and signs associated with obstruction of individual arteries, works on neurology should be consulted. In cerebral hæmorrhage, as has been said, coma is usual, and it may be possible to localize the lesion by deviation of the head and eyes, absence of movement of limbs, flaccidity followed by rigidity, absent followed by increased tendon reflexes and by a positive Babinski response on one or other side. Such patients who recover may show a permanent motor or sensory defect, such as a hemiplegia; and many show in addition a personality change which may amount to dementia. In thrombosis, when consciousness is so often retained, the motor or sensory paralysis is the chief feature of the attack, hemiplegia, monoplegia, aphasia, hemianopia, pins and needles in half the body, sensory loss, or the highly complex syndromes which follow occlusion of a vessel such as the posterior inferior cerebellar artery, may occur. As a rule these defects are maximal very soon after the onset ; occasionally they progress in stages, suggesting propagation of clot to the branches of the vessel. There is always some recovery, which may be complete in as

short a time as a few minutes, or may slowly improve over a period as long as eighteen months. The quick return of function is attributed to return of blood supply through collateral channels. The later recovery is doubtless attributable to recovery in function of nervous tissue temporarily interrupted by ischæmia, some to the transfer of function to other neurones, and some to re-education of those remaining functions which can be substituted for those that have been lost. Thus, *inter alia*, the degree of recovery depends on age, being greater in young subjects than in old, and on the speed and resolution with which re-educational measures are instituted.

The detailed pathology of these lesions is far from well understood. In cerebral hæmorrhage the brain is often so disrupted that it is often impossible to locate the actual vessel from which the leak began, much less to identify the nature of the lesion; while in cerebral thrombosis, death commonly occurs so late after the attack that the nature of the lesion is uncertain. Cerebral hæmorrhage is, I think, more common in subjects with very high pressures, and such is supported by the figures of Table 12.3 which were, however, collected at a time

TABLE 12.3. *Height of Systolic Blood Pressure in Relation to Cause of Death (Janeway, 1913).*

	Median of Special Group	Percentage at or below Median (220) for Whole Group	Percentage above Median (220) for Whole Group
Cardiac insufficiency	210	68.3	31.7
Uræmia (gradual and coma)	220	52.1	47.9
Cerebral apoplexy	225	41.4	58.6
Angina pectoris	200	80.0	20.0
Oedema of lungs	240	28.6	71.4
Acute infectious disease (mostly pneumonia)	185	84.6	15.4

there is no need to suppose that the vessel has been subjected to unusual strain; though emotional rises of blood pressure may occur at such times. It is likely, therefore, that it is the actual weakening of the vessel wall that is the determining factor. Jores (1904) in his classical paper on arterial lesions in hypertension found degenerated arteries fairly regularly in brains which showed old or fresh apoplectic insults; frequently there were solitary aneurysms associated with pronounced degeneration of the arterial wall. Some of these medial

tion which seem to have been helpful to me are therefore offered with diffidence. The attack in cerebral hæmorrhage tends to show the following features : (a) headache is often conspicuous at the onset, and after the patient recovers consciousness, if he does so ; (b) consciousness is usually lost soon after the onset ; (c) more than half never recover consciousness but die in the attack ; (d) neck rigidity is sometimes striking, developing some four hours after the onset ; (e) the cerebrospinal fluid is often blood-stained ; (f) the phenomena of compression of the brain, a slow irregular pulse and Cheyne-Stokes respiration are not uncommon. Similar phenomena occur in subarachnoid hæmorrhage, from which intracerebral hæmorrhage has to be distinguished ; whereas in intracerebral hæmorrhage focal signs are those of interference with cerebral tissue, in subarachnoid hæmorrhage these signs arise largely from cranial nerves, particularly the oculomotor nerves. Conversely, cerebral thrombosis tends to show the following : (i) headache is rather uncommon, (ii) consciousness is frequently retained, though in a large lesion it is lost, (iii) more than half the patients recover from their attack, (iv) neck rigidity is absent, and (v) the c.s.f. is not blood-stained. Cerebral embolism has features precisely similar to those of cerebral thrombosis, but its onset is invariably sudden and it cannot be diagnosed in the absence of a source for the embolus. In hypertension, auricular fibrillation and myocardial infarction provide the only two such sources that are not extremely rare.

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hemianesthesia, etc., which quickly and, sometimes, abruptly, clears in the course of a few minutes, consciousness being frequently unimpaired throughout. Such attacks have been attributed for many years to cerebral angiospasm. This is an explanation that I could never reconcile with the known behaviour of the cerebral arteries. The hypothesis implies that suddenly, and without a recognizable stimulus, one artery contracts so strongly that blood flow through it ceases, while all the other arteries remain open. This would have been unlikely enough, but add that the vessel in question is a cerebral artery which is known to belong to one of the least reactive groups in the body, and the whole hypothesis can only be described as grotesque. It was with some interest, therefore, that I observed and collected clinical records of exactly similar attacks occurring in patients with normal pressures, but having auricular fibrillation and mitral stenosis, the common sources of arterial emboli. In hypertension and in cerebral embolism there is every gradation between attacks in which paralysis is extensive and permanent to those in which it begins and ends abruptly, lasting a few minutes in all. If such transient attacks can occur when an artery is occluded by an embolus, why should they not occur when the same artery is occluded by a thrombus or by an aneurysm?

(J. Neurology, 1948, 1951a) there were two cases which I could not explain, the one a woman of 41 with mitral stenosis and auricular fibrillation but not hypertension, who had nine attacks of transient left hemiparesis over a period of five years and then five years of freedom, the other a man of 62 with mild hypertension who had three attacks.

The answer to this

who drew attention first described by Egas Moniz and others (1937). In this syndrome it is common to get repeated attacks of transient paralysis arising from the area supplied by the middle cerebral on the same side, as well as transient attacks of blindness in the eye on the same side. Denny-Brown's case IV had several attacks of left hemiparesis. Johnson and Walker (1951) have collected 107 cases in which this lesion has been diagnosed. Many of them occurred in young subjects not

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degenerations are, as we have seen, partly a manifestation of age. The arteriolar necroses of the malignant phase are, however, not so dependent on age, and it is tempting to suppose that they may be responsible for the cerebral hæmorrhage that so often terminates the life of a young person with chronic nephritis or pyelonephritis, or older subjects in the malignant phase of essential hypertension. The events precipitating thrombosis of a vessel are no better understood in the brain than in the heart. Almost always the thrombosis forms at a point where the artery is greatly narrowed by intimal thickening, which is probably atheromatous in origin in most cases. The arterial pressure may be at any level in cerebral thrombosis.

Russell (1954) has analysed 461 cases of spontaneous intracranial hæmorrhage having necropsies at the London Hospital in the period 1912 to 1952 (Table 12.4). Hypertensive cases comprised about half the total. It is to be noted, however, that cerebral thrombosis, which

TABLE 12.4. *Analysis of Necropsy Records of Intracranial Hæmorrhage at London Hospital, 1912-1952 (Russell, 1954).*

I. Hypertensive	232
II. Congenital medial defects in cerebral arteries (92 cases with aneurysm)	96
III. Blood diseases	36
IV. Mycotic aneurysm	28
V. Vascular hamartoma	21
VI. Arteritis (no aneurysm)	13
VII. Neoplasms	9
VIII. Arterial degeneration (no cardiovascular hypertrophy)	7
IX. Various	3
X. Cause not found	16
Total	461

is also frequent in hypertension, is not included. In the hypertensive cases the basal ganglia were affected in 151; a frequency attributed to the tendency in benign hypertension for muscle to be replaced by fibrous tissue in the perforating cerebral arteries of this region. She found fibrinoid necrosis in malignant and nephritic hypertension, chiefly in the vessels of the pons which is one of the chief sites of cerebral hæmorrhage in these conditions.

"Transient Cerebral Attacks" or "Little Strokes"¹

A great deal of controversy has surrounded attacks in which there is sudden paralysis of a limb or of speech or of vision, a hemiplegia, a

¹ A most appropriate term used by Alvarez (1951).

know that cardiac arrest of a few seconds produces loss of consciousness and, of a few minutes, permanent dementia.

Thus the consequences of an organic occlusion of a cerebral artery depend on its size, its site, and on the adequacy of collateral circulation. If it supplies an area such as the motor area of the cortex or the internal capsule, the effects of interruption will be profound; if its collateral supply is good the paralysis may be quite transient; so may it, if these motor areas are at the periphery of the infarct, for blood supply to these may quickly return even though the centre of the lesion dies and is replaced by a small blood cyst. It follows from this argument that thrombosis of small arteries supplying the so-called silent areas of the brain may produce attacks that are so slight as to escape recognition. Many such attacks may destroy considerable areas of cerebral substance leaving numerous small or large cysts filled with altered blood, a condition called porencephaly. Such patients gradually lose their memory and become disorientated, presenting finally the picture of arteriosclerotic dementia.

One of the most illuminating reports on the brain in hypertension is that by Rosenberg (1940), who examined seventeen brains from malignant hypertension and fifteen controls. In the cases of hypertension, massive cerebral hæmorrhage was found in four cases and small and spotty hæmorrhages with numerous infarcts of similar size in five cases. Single large infarcts occurred in three cases. He was impressed with the frequency of multiple miliary infarcts which he found in 12 cases in the basal ganglia, cortex, white matter, brain stem and cerebellum, varying in size from 6 mm. across to minute softening only seen with a microscope. In most of these he could not identify the occluded vessel but he found some infarcts adjoining thrombosed vessels. He suggested that cerebral symptoms were of three kinds in malignant hypertension: (1) due to increased intracranial pressure (headache, vomiting, drowsiness), (2) due to multiple miliary cerebral lesions, a wide variety of transient disturbances often without physical signs, and (3) due to large cerebral vascular accidents.

Generalized Cerebral Vascular Disease

Generalized vascular disease has been alluded to already. The distribution of the arterial lesions, the subsequent arterial thrombosis and destruction of small areas of brain determine the clinical picture. If the motor and sensory tracts are spared, the defect is one of memory, intellect and personality ultimately leading to dementia. If localized in the region of the corpora striata, "arteriosclerotic muscular rigidity" is the outcome. Finally, bilateral lesions in the region of the internal capsules produce "pseudobulbar palsy". It is, however, by no means certain that all the cerebral lesions of old age that are attributed to

treatment for aneurysms of the internal carotid artery and its neighbouring arteries of the Circle of Willis. In 150 ligatures of these vessels by Jefferson (1952) and Johnson (1952) only 11 showed hemiplegia, transient in four. It is conceivable that some of these attacks are due to small pieces of clot detached from the main mass and passing distally as emboli, by a mechanism similar to that suggested by Lewis and Pickering (1934) for the digital gangrene resulting when the subclavian artery was damaged by a cervical rib. It is also possible, but less likely, that each episode represents a further propagation of clot. There is, however, another explanation, namely, that the presence of an arterial thrombus in a main vessel acts as a permanent hindrance to blood flow, not enough to produce ischaemia when the arterial pressure is high, but adequate when, for any reason, arterial pressure is reduced. Denny Brown described the supervention of paralysis in one of his cases when arterial pressure was reduced by a vasodilator drug. A more striking case was described by Adams (1954) of a 56-year-old man with cirrhosis of the liver who bled and developed a left hemiparesis. He was transfused, the blood pressure rose and his hemiplegia disappeared. He bled again and the hemiplegia returned, death occurring forty-eight hours later. At necropsy extensive atherosclerosis of the cerebral arteries was found. The lumen of the right middle cerebral artery was narrowed to 0.5 mm. by a plaque, but was patent; the nerve cells of the hemisphere showed ischaemic changes. Similar cases have been described by Corday, Rothenberg and Putnam (1953) under the term Cerebral Vascular Insufficiency. Eastcott, Rob and I (1954) have recently described a woman who had no less than thirty-two attacks in each of which she developed a right hemiparesis and loss of vision in the left eye without loss of consciousness. An atheromatous constriction was found at the origin of the left internal carotid. Excision of this and repair of the artery abolished the attacks. Each of these attacks was preceded by palpitations, suspected but never proved to have been paroxysms of tachycardia.

It seems, therefore, fair to conclude that these transient attacks or little strokes are due to organic vascular occlusion and not to cerebral artery spasm. There is known to be a fairly free anastomosis between the cerebral arteries not only in the Circle, but over the hemispheres and also at the capillary level (for evidence, see Pickering (1948)). Shepherd (1950) has shown that when the femoral artery is occluded in the groin, the blood flow through the calf falls to zero at once, is re-established within thirty seconds and rises to its original level by the fourth minute. Comparable observations have not been made on the cerebral circulation. Nor do we yet know much about the duration of ischaemia that is necessary to produce temporary or permanent loss of function in the constituent tissues of the hemisphere, though we

know that cardiac arrest of a few seconds produces loss of consciousness and, of a few minutes, permanent dementia.

Thus the consequences of an organic occlusion of a cerebral artery depend on its size, its site, and on the adequacy of collateral circulation. If it supplies an area such as the motor area of the cortex or the internal capsule, the effects of interruption will be profound; if its collateral supply is good the paralysis may be quite transient; so may it, if these motor areas are at the periphery of the infarct, for blood supply to these may quickly return even though the centre of the lesion dies and is replaced by a small blood cyst. It follows from this argument that thrombosis of small arteries supplying the so-called silent areas of the brain may produce attacks that are so slight as to escape recognition. Many such attacks may destroy considerable areas of cerebral substance leaving numerous small or large cysts filled with altered blood, a condition called porencephaly. Such patients gradually lose their memory and become disorientated, presenting finally the picture of *arteriosclerotic dementia*.

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is the outcome. Finally, bilateral lesions in the region of the internal capsules produce "pseudobulbar palsy." It is, however, by no means certain that all the cerebral lesions of old age that are attributed to

"arteriosclerosis" are indeed vascular. Hughes, Dodgson and MacLennan (1954) have recently described 51 cases of chronic cerebral vascular disease in patients with high blood pressure. Most of the patients were old, but in some the history extended into middle age. Intellectual deterioration occurred in every case, sometimes following major cerebral insults, sometimes following little strokes and sometimes without any obvious attack. Emotional lability was striking. Pseudobulbar palsy developed in eight. Various signs of involvement of pyramidal and extrapyramidal systems were common. The brain was examined after death in 15 cases, and showed multiple small lesions representing different stages in the organization of areas of ischaemic softening, particularly numerous in the caudate nuclei.

HYPERTENSIVE FITS

Fits, presenting some resemblance to "grand mal," may occur with a cerebral haemorrhage, but are most often seen as a manifestation of a severe hypotension of comparatively recent onset, such as is found in acute nephritis, "toxæmia" of pregnancy, and in some cases of the malignant phase of hypertension. Three brief case records (Pickering, 1934) illustrate the features of this condition.

Case 1. A woman of 34 years, lost the sight of her right eye and her ability to speak, and became drowsy three hours before the onset of her third labour on March 30th, 1931. Labour was otherwise uneventful and lasted six hours. Her systolic blood pressure was 190 mm. Hg, she had slight cedema of the legs and arms, and her urine contained much albumen; the blood urea was 43 mg. per cent. She remained drowsy until April 3rd, when she recovered; by this time the cedema had disappeared, but the hypertension persisted; the fundi were normal, but the left fundus showed a small area of exudate with drooping of the left, abnormal.

in both eyes. About 4 p.m. on May 25th she became drowsy and comatose, and there was conjugate deviation of the eyes to the right. Lumbar puncture at 7 p.m. was followed by two generalized convulsions and coma which lasted about twelve hours. Two similar attacks occurred on May 30th and June 30th. Albuminuric retinitis was disappearing on October 10th and had resolved by May 26th, 1932, leaving consecutive optic atrophy and pigmented spots in the retina. Hypertension and the presence of albumen and casts in the urine persisted throughout, but there was never any rise in the blood urea. She died November 2nd, 1932.

in both eyes. She became drowsy with the onset of her menstrual period, and came comatose and had three epileptiform convulsions. Coma lasted fifty-six hours in all and recovery from it was complete. The systolic blood pressure was 190 mm. Hg, the blood urea was 90 mg. per cent. There were numerous granular casts and much protein in both eyes. She experienced no further attacks of menstrual generalization.

convulsions, each lasting about two minutes; Babinaki's sign was positive on both sides. Recovery from this state was complete on December 25th, 1930. On January 29th, 1931, during the next menstrual period she again became comatose and had convulsions; recovery was complete, apart from severe headache, by January 30th. In the menstrual period of February, 1931, she became drowsy for two days and complained much of headache, but had no fits. During the disturbances of December, January and February, the blood urea was normal, and the blood diazo reaction was negative. From this time there were no further convulsions, nor did she again become comatose until she died.

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but presented no other

abnormal signs in the central nervous system. He had a systolic blood pressure of 190 mm. Hg and a blood urea of 110 mg. per cent.; the urine contained albumen, granular casts and blood. There was no retinitis. At 1 a.m. on October 3rd, 20 ml. of cerebrospinal fluid were removed by lumbar puncture; the pressure was not measured but was thought to be increased. Five epileptiform fits followed in quick succession and by 2 a.m. the temperature had risen to 103° F. At 11.30 a.m. the temperature had fallen to 102° F., he was a little less drowsy, and lumbar puncture was repeated. The fluid rose to a height of 250 mm. in the manometer tube, and showed small pulse but no respiratory oscillations. After removal of 1 ml. of fluid the pressure fell to 100 —

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On at autopsy, small orange exudates were present in both retinas. He died on October 8th, 1932. Autopsy showed polyarteritis nodosa affecting the heart and pancreas slightly and the kidneys extensively.

Case 1 suffered from toxemia of pregnancy and post-toxemic hypertension; Case 2 from malignant hypertension associated with an atrophic kidney due to obstruction of the renal artery; Case 3 from polyarteritis nodosa.

These attacks obviously represent a very generalized disturbance of cerebral function, which may be so slight as to provoke no more than headache, drowsiness and irritability, and may affect one part of the brain more than another, so that a focal loss of function precedes the attack. They were at one time attributed to uræmia, but there is now general agreement that this is not so. There are two possibilities, namely—

and Töppich (1921) and Blackfan and Hamilton (1925), in which evidence for swelling of the brain was obtained during life or after death. On the other hand, in Cases 1 and 2 (Pickering, 1934), the cerebrospinal fluid pressure was the same during the coma following

■ fit as when the patient was quite alert and free from headache ; in the third case, of course, it could not be measured. Evidence for generalized arterial contraction has been obtained by Byrom (1934), who has shown that in rats with hypertension, due to renal artery constriction, convulsions are associated with spasmodic constriction of the cerebral arteries associated on the one hand with arteriolar necroses and on the other with cerebral oedema (Chapter 5). Byrom believes that the cerebral arterial spasm is ■ consequence of the grossly raised intravascular pressure. This interpretation conforms with the two features of the human attacks : (a) that they are often preceded by an acute rise in arterial pressure, and (b) that the attacks may be relieved by drugs which lower arterial pressure, e.g. hexamethonium and veratrum alkaloids, even though these drugs, which act via the sympathetic nerves must be regarded as having little action, direct or indirect, on cerebral vessels.

URÆMIC CEREBRAL SYMPTOMS

In the terminal stage of renal failure, very complex disturbances occur in the composition of the blood which may produce profound cerebral disturbances. The first is usually vomiting, which may occur intermittently for weeks or months before the final phase. In the final phase the patient is usually drowsy, may be irritable or disorientated, may have repeated convulsions and finally lapses into deep coma with positive Babinski responses. Spontaneous muscular twitching and gross exaggeration of the tendon reflexes are common findings.

HYPERTENSION AND THE HEART

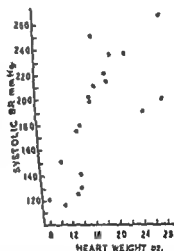
As Table 12.1 shows, by far the commonest mode of death in patients with hypertension is cardiac. The termination takes three forms, cardiac failure of the congestive type, which is by far the commonest, left ventricular failure, and myocardial infarction. In Janeway's series (Table 12.2) cardiac failure accounted for sixty deaths, " angina pectoris " for ten and oedema of the lungs for seven.

Cardiac Hypertrophy

In experimental animals, persistent hypertension produced by renal artery constriction is associated with cardiac hypertrophy, which is approximately proportional to the height of the arterial pressure (Fig. 5.5). Evans (1921) also found that in man the degree of cardiac hypertrophy was related to the height of the arterial pressure (Fig. 12.3) The truth of this does not imply the converse. Enlargement of the heart cannot be accepted, as is so often done by pathologists, as ■ sure indication of hypertension during life. Coronary sclerosis can produce an increase in weight to an average of 550 g. irrespective

of the arterial pressure (Bartels and Smith, 1932 ; Davis and Blumgart, 1937 ; Harrison and Wood, 1949) Assessed during life there is also a relation between cardiac size and blood pressure. In Bechgaard's (1946) series the percentage of patients showing radiological evidence of increased cardiac size rose from 31 per cent. of those with systolic pressures between 140 and 159 mm. Hg, to 65 per cent. of those whose pressures exceeded 240 mm. Roentgenograms reveal a tendency

FIG 12.3. Relation systolic blood pressure to heart weight in patients dying of hypertension with renal disease. (After Evans (1921), *Quart J Med*, 16, 215).



nearest capillary, and is therefore likely to exhibit a lower oxygen tension and a higher concentration of metabolic end products than occurs in muscle fibres of subjects with lower pressures.

Cardiac hypertrophy in hypertension affects almost exclusively the left ventricle, except in such cases (by no means uncommon) in which chronic bronchitis and emphysema are associated findings and in which the elevated pulmonary artery pressure is associated with a hypertrophy of the right ventricle ; and in the later stages of congestive failure when the same sequence would seem to occur (Harrison and

is estimated (a) by the extent to which the cardiac impulse is displaced out and down, and (b) by the movement of the chest wall in the region of the impulse, and particularly by the extent to which the heart moves the ribs. In other types of heart disease, the degree of enlargement, assessed clinically, has been shown to be one of the most important factors affecting prognosis (Grant, 1933). That the same is true for hypertension is shown by Janeway's (1913) figures (Table 12.5). In his follow-up of 1,000 cases of heart disease for ten years, Grant (1933) found that the following factors adversely

TABLE 12.5. *Evidence of Cardiac Hypertrophy in 437 Patients* (Janeway 1913) (based on physical examination only).

	Dead	Living
None . . .	8	89
Questionable . . .	4	5
Slight . . .	41	98
Moderate . . .	96	83
Marked . . .	44	19
Total . . .	193	294*

* Janeway gives 244 for this total, presumably a misprint.

affected prognosis : cardiac size, exercise tolerance, previous attacks of failure, venous congestion and auricular fibrillation.

Congestive Cardiac Failure

In this, the commonest form of heart failure, the heart fails as a whole. In heart failure in general the cardiac output may be high, normal or low, but the heart is always working at a high venous pressure. In heart failure occurring in hypertension, the cardiac output is usually reduced. The high pressure in the left auricle produces engorgement of the pulmonary veins and capillaries, rigidity of the lungs, a low vital capacity, and thus breathlessness; the high pressure in the right auricle produces distension of the neck veins, engorgement of the liver, and, by a process not yet fully understood, retention of water and sodium by the kidney with cedema of the dependent parts, ascites and hydrothorax. This is the final picture.

The first symptom is usually breathlessness on exertion. This remains stable for long periods, but it is, in general, progressive, usually rather gradually, but sometimes in steps which may or may not be associated with recognizable causes such as infection, onset of auricular fibrillation or myocardial infarction. Decrease in exercise tolerance is succeeded by cedema of the feet at the end of the

day, which disappears by morning and ultimately by more generalized edema and anasarca. Goldring and Chasis (1944) summarize their experience of cardiac failure in hypertension as follows: "In our group of 139 deceased patients, 77 per cent were in congestive heart failure at some time during their course. These patients lived an average of 1.8 years from the first evidence of congestive heart failure; 57 per cent died of their heart disease within one year of the onset of heart failure and only 24 per cent were alive three years after the onset of heart failure. . . . Episodes of congestive heart failure sufficiently severe to confine the patient to bed in the hospital occurred an average of 2.3 times between the first failure and death; in only 15 per cent of the group did three or more such episodes occur before death."

Left Ventricular Failure; Cardiac Asthma; Paroxysmal Nocturnal Dyspnoea

In this condition breathlessness is paroxysmal, mainly nocturnal, and the patient often dies in an attack, the lungs being grossly oedematous *post mortem*. The typical attack occurs when the patient is in bed at night. It may come on soon after he lies down, but more usually wakes him about a half to one hour after he has gone to sleep. He wakes feeling suffocated, and unable to get enough air into his chest. This quickly gets worse, the patient sits up, gets out of bed, and struggles to the window, which he opens to get more air. He is terrified that he is going to die. His face is pale and anxious, the pupils dilated, the skin covered with sweat. The breathing is fast, laboured and shallow, with no especial difference between inspiration and expiration, although in some cases there is a special difficulty in emptying the chest, as in bronchial asthma. The pulse is small and fast, the blood pressure higher than usual for the patient. Pulsus alternans and gallop rhythm are almost invariable. Unless the attack is relieved, the patient becomes cyanosed; rales, which are always audible on auscultation, become audible at a distance; pink frothy sputum may well out of the mouth; respiration becomes feebler and finally stops, the whole episode having taken perhaps ten to sixty minutes. Similar attacks are sometimes associated with . . .

adequate treatment.

These attacks are thought to represent left ventricular failure because they occur largely in maladies primarily straining the left ventricle, hypertension, aortic regurgitation and occasionally in

œdema. It is thought that the cause of breathlessness at the beginning of an attack is a rise in left auricular and pulmonary venous pressure, with consequent rigidity of the lungs and reduced ventilation. It seems likely that the patient is already partly asphyxiated when he wakes, and the alarm further raises arterial pressure and increases left ventricular load.

As Table 12.3 illustrates, patients who develop cardiac asthma usually have very high pressures; they often present *pulsus alternans* and gallop rhythm between the attacks. It seems probable that in them the left ventricle has reached something very near to the limit of its capacity for work, and that further demands raise considerably the venous filling pressure. That emotion or sexual intercourse should precipitate left ventricular failure will occasion no surprise in view of the very powerful effects of such stimuli on arterial pressure. What is surprising is that sometimes such subjects have a fair exercise tolerance. What is almost astonishing is that the attacks characteristically occur at night when the patient is asleep. That lying down raises the venous inflow to and output from the heart is known (McMichael, 1938), but this is a small effect as compared with that of exercise. It is possible that in such subjects the large rises of arterial pressure described by MacWilliam (1923) occur during sleep (see Chapter 3), but this has not been proved. In fact cardiac asthma remains somewhat of an enigma (see Harrison, 1939; Fishberg, 1940).

Cardiac asthma may occur in patients whose blood pressure runs within the range commonly accepted as normal or at any higher level, but is undoubtedly commonest and most severe in patients with very high pressures and thus in the malignant phase. In subjects with low pressures and without valvular disease, the left ventricle is usually extensively infarcted.

Angina Pectoris and Myocardial Infarction

Here the dominant symptom is pain, typically felt deep in the centre of the chest, radiating across the chest, down one or both arms, particularly the left, into the neck and angle of the mouth, or occasionally confined to a peripheral part of this distribution or to the abdomen. The pain is often associated with a sense of constriction or of being choked or suffocated, which is the origin of the term angina. In the classical angina of effort, or Heberden's angina, the pain comes on exercise and becomes so severe that the patient stops; the pain then subsides in a few minutes and exercise is resumed. It is known, since Lauder Brunton first demonstrated it, that the pain is relieved by nitrites, particularly amyl nitrite and glyceryl trinitrite, which are vasodilators. In coronary thrombosis, more properly termed myocardial infarction, the pain may begin at rest or during exercise and

lasts for many minutes or for one or more days. It is not relieved by nitrites, but is relieved by morphine. During the attack, the patient may sweat and vomit and in extreme cases consciousness may be lost, the pulse is slowed and the arterial pressure falls—effects which may possibly be due to the Bezold reflex (see p. 54). Cardiac arrhythmias are common, and the patient may die of ventricular fibrillation. Afterwards fever, leucocytosis, a raised sedimentation rate, a pericardial rub, congestive failure, and changes in the electrocardiogram are common.

So far as we know the pain in such cases is analogous to that of intermittent claudication, in which substances released from the muscle fibres during contraction and normally removed by the circulating blood, accumulate in the absence of adequate blood flow, and stimulate pain nerve endings (Lewis, Pickering and Rothschild, 1931). In angina of effort, the blood supply is adequate at rest, inadequate during exercise. In myocardial infarction blood flow is inadequate at rest, and pain continues until the nerve fibres in the infarcted area cease to conduct.

Thanks to the work of Blumgart, Schlesinger and Zoll (1941), it is now known that in the vast majority of both types of pain the anatomical basis is occlusion of one, or more than one, main coronary artery. In their series of 355 cases, in which both coronary arteries were injected with radio-opaque material and examined by radiography and subsequent dissection, complete occlusion of one or more coronary arteries was found in 38 cases without a history or signs of heart disease, and in all of 38 cases in which angina of effort was the chief symptom. Nine cases with valvular disease or cor pulmonale, and enlarged hearts in which angina had been a subsidiary symptom, had gross coronary narrowing but no occlusion. In all cases with angina pectoris during life, but no complete occlusion, the heart was hypertrophied. Whether or not symptoms arise as a result of coronary occlusion depends on the efficiency of the collateral circulation, and this depends on the speed of the occlusion. If the occlusion is preceded by a slow arterial narrowing of substantial dimensions, the symptoms may be

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pain. Thus is explained the fact, which I had long observed, and which had previously perplexed me, that angina pectoris, like intermittent claudication, frequently begins suddenly. Between these clear-cut examples there are, of course, intermediate

example, those in which there is no occlusion but the phenomena of anginal pain or myocardial infarction are induced by a profound fall of blood pressure occasioned by hæmorrhage or by other agencies, e.g. sympathectomy or vasodilator drugs, which profoundly reduce arterial pressure and thus the head of pressure at which grossly narrowed, but not occluded, coronary arteries are perfused. In fact, the range of attacks produced by disease of the cerebral arteries and by those of the coronary arteries is strikingly similar. In both cases the hypothesis of arterial spasm has been inferred to explain some of these attacks; in neither is there yet any legitimate ground for supposing this hypothesis to be correct (Pickering, 1951b).

Finally, in extensive disease of the coronary arteries, isolated patches, or more diffuse lesions, of myocardial fibrosis are common. These lesions probably represent areas in which muscle fibres have been killed by ischæmia and replaced by fibrous tissue. They are, perhaps, the counterpart of the numerous small cysts of the brain which result from similarly widespread disease of cerebral vessels

Arterial Pressure in Coronary Artery Disease

Most workers have concluded that hypertension plays an important part in coronary artery disease. Master, Jaffe, Dack and Silver (1943) accepting 150 mm. Hg systolic and 96 mm. Hg diastolic as hypertension found that 69 per cent. of all patients had suffered from hypertension before the coronary artery occlusion had occurred. In Cassidy's (1946) series of 1,000 cases, 44.6 per cent. had pressures

TABLE 12.6. *Blood Pressure in Coronary Occlusion (Master, 1953).*

	Total		Hypertensive (Percentage Age Group)	Borderline, (Percentage Age Group)	Normal (Percentage Age Group)
	No.	Percentage Total			
500 men age					
25-39 .	27	5.4	22.2	—	74.1
40-44 .	77	15.4	26.0	3.9	70.1
45-49 .	90	17.9	25.6	5.6	68.8
50-54 .	128	25.6	27.3	4.7	68.0
55-59 .	115	23.0	28.7	8.7	62.6
60-64 .	63	12.6	30.4	11.0	58.6
100 women age					
35-49 .	22	22.0	63.7	—	27.3
50-54 .	18	18.0	77.8	0	22.2
55-59 .	28	28.0	64.4	10.6	25.0
60-64 .	32	32.0	78.2	9.3	12.5

below 160/100, 33.7 per cent. had pressures between that figure and 200/120, and 21.7 per cent. had pressures higher than 200/120. None of these series, however, takes account of age which, as was seen in Chapter 8, is a most important factor in determining arterial pressure. Using the limits of normal blood pressure and hypertension which he and others (1952) have advocated and which are shown in Table 8.6, Master (1953) has reviewed the incidence of hypertension in 600 private patients with coronary occlusion under the age of 65 years. His results for 500 men and 100 women are given in Table 12.6. Master concludes that hypertension, if it is a factor at all, is not the all-important one in men who sustain coronary occlusion, while it is a very significant factor in women. In interpreting these figures of Master, the reader should remember that, according to his system, 95 per cent. of the pressures met with in a representative sample of the population are regarded as normal, 2.5 per cent. as hypertension. It will be seen, therefore, that there is a distinct tendency for the arterial pressure to be raised in both men and women with coronary disease, but this is much greater in women.

Pathogenesis of Cardiac Lesions in Hypertension

Cardiac hypertrophy can legitimately be interpreted as a work hypertrophy analogous to, and apparently proportional to (p. 223), the hypertrophy of the media of the muscular arteries. This hypertrophy probably serves a useful function, since acute rises of blood pressure occurring in man, as from a pheochromocytoma (see Chapter 20) may produce death from left ventricular failure. In the experimental animal section of all four moderator nerves on the same day produces an acute rise of arterial pressure which kills most of the animals.

... is attributed to a further rise of arterial pressure above the levels previously sustained by that patient without symptoms, for it is the general experience that no such rise in the general level of arterial pressure accompanies or precedes the final breakdown. It is a tempting, and very generally held, hypothesis that the onset of cardiac failure represents the superaddition of myocardial ischaemia consequent on the arterial disease induced or abetted by the hypertension. This view is clearly expressed by Fishberg (1940): "The underlying basis on which heart failure in essential hypertension develops would thus appear to be relative ischaemia of the left ventricle. This results from the coincident operation of two pathogenic factors, namely, hypertrophy of the left ventricle with resultant need for more ample blood supply, and limitation of blood

flow to the left ventricle due to arteriosclerosis of the coronary vessels." On this view the supervention of cardiac failure in a subject with a stable hypertension would be due to the steady advance of arterial disease limiting blood flow to the heart. This explanation remains attractive and though it is not supported, it cannot be said to be finally excluded by facts subsequently elicited.

The fact that cardiac hypertrophy is accompanied by increased muscle fibre size, and that blood vessels lie between muscle fibres, explains the findings of Gross and Spark (1937) that the average number of arterioles per low power field diminishes in inverse proportion to the weight of the heart. This is presumably a stable situation, and what we are in search of is a progressive lesion. Elastosis and arteriosclerosis, the two common conditions producing narrowing of the

TABLE 12.7. *Incidence of Marked Coronary Disease postmortem in Men and Women with and without Hypertension* (Davis and Klainer, 1940a).

Age	Percentage Incidence of Marked Coronary Disease			
	Without Hypertension		With Hypertension	
	Male	Female	Male	Female
30-49 . . .	21.9	3.7	55.4	20.0
50-59 . . .	29.2	5.0	40.9	28.6
60-69 . . .	35.6	21.7	48.5	37.5
70+ . . .	30.9	33.3	50.0	31.6

Hypertension represents arterial pressure over 150/90.

smaller arteries and arterioles in the benign phase of hypertension, are not conditions frequently or diffusely affecting the vessels of the heart. In the malignant phase arteriolar necroses occur in the heart, but are not very frequent. It is evidently to the atheromatous intimal thickening of the larger arteries that we must look for the probable cause of a progressive myocardial ischaemia. Here the injection of radio-opaque material, as developed by Gross (1921), and by Blumgart, Schlesinger and Davis (1941), have been of great assistance and yielded the following results relevant to our present problem.

The incidence of marked coronary sclerosis *post mortem* in men and women with and without hypertension in the Beth Israel Hospital, Boston, is shown in Table 12.7. In subjects without hypertension gross coronary disease is much commoner in males than females in the fourth, fifth and sixth decades; the disparity becomes small in the seventh and vanishes in the eighth; the incidence rises slowly in males

to the seventh decade, and much more steeply in females throughout. In subjects with hypertension, the incidence of severe coronary disease is higher in males than females throughout; the peak incidence in males is reached thirty to forty-nine and remains steady thereafter; in females it is lower and occurs later in life. It should be remembered, however, that these patients who died. They show, in fact, that the incidence of

interesting to compare them with the mortality from cardiovascular renal diseases for the United States as a whole (Table 12.8). It is tempting to suppose that the greatly

TABLE 12.8. *Death Rates per 100,000 Population from all Causes and from the Principal Cardiovascular-Renal Diseases, by Age, for White Males and White Females (Goldring and Chassis, 1944).*

Age Group	Males		Female		Percentage Cardiovascular Renal of Deaths from All Causes	
	All Causes	Cardiovascular-Renal Diseases	All Causes	Cardiovascular-Renal Diseases	Males	Females
Total, 1 to 74 years .	878.0	325.0	632.0	242.9	37.0	37.3
1 to 4 years .	403.9	6.8	354.8	6.7	1.7	1.9
5 to 9 years .	178.2	10.3	142.3	9.3	5.8	6.5
10 to 14 years .	139.9	16.2	103.4	18.8	11.6	17.8
15 to 19 years .	208.0	21.4	166.6	21.8	10.3	13.1
20 to 24 years .	291.4	29.0	263.2	30.6	10.0	11.4
25 to 34 years .	417.1	59.5	316.5	50.2	14.3	14.5
35 to 44 years .	774.7	179.9	519.3	124.5	23.2	24.0
45 to 54 years .	1,600.7	559.5	1,025.8	366.0	35.0	35.7
55 to 64 years .	3,299.3	1,546.7	2,302.5	1,077.0	46.9	46.8
65 to 74 years .	6,750.9	3,933.0	5,378.3	3,161.7	58.3	58.8

increased death rate of males over females from 35 to 64 years is partly due to the increased incidence of coronary disease in men. Such a supposition would also partly explain the more favourable prognosis in women than in men with similar degrees of hypertension and the greater percentage of males than females dying a cardiac rather than another type of death in Janeway's (1913) series (Table 12.2).

Two pieces of work are difficult to reconcile with this hypothesis. Davis and Klainer (1940d) compared the coronary arteries in patients dying in congestive failure, of whom 49 had hypertension and 25 had not, rheumatic, syphilitic, thyrotoxic and pulmonary heart disease and diabetes were excluded. Marked coronary artery disease was found in 23 out of 25 patients without hypertension, but in only 26 of 49 patients with hypertension. Harrison and Wood (1949) injected the

coronary arteries in the hearts of 15 patients who had had angina or myocardial infarction before death, classed as ischaemic heart disease whatever the blood pressure, and of 27 patients who had had gross hypertension; of these 27, four had had no cardiac symptoms, six had had effort dyspnoea only, six had had left ventricular failure, but died of another cause, and 11 congestive cardiac failure. They concluded: "The coronary arteries vary sharply between hypertensive and ischaemic cases; in the former they are large with smooth bores, in the latter they are narrow and frequently occluded." Detailed inspection of their results shows that in fact coronary disease was commoner in those who died of congestive failure and left ventricular failure than in those with effort dyspnoea only, or those without cardiac symptoms. Right ventricular hypertrophy was usual in those with congestive failure but occurred irregularly in the remainder, suggesting that prolonged slight left ventricular failure leads to increased pulmonary artery pressure and right ventricular hypertrophy.

Perhaps the dilemma is in part resolved by Davis and Klainer's (1940c) studies on the coronary arteries of 61 patients who had had angina pectoris during life. Of these 40 had had hypertension (blood pressure 150/90 and over) and 21 had not. There were 52 males of whom 60 per cent. had had hypertension and nine females of whom 90 per cent. had had hypertension. Occlusion of one or more coronary arteries was found in 22 (55 per cent.) of the 40 patients with hypertension who had had angina, and in 10 (90 per cent.) of 21 patients with normal pressures who had had angina. Assuming, as seems legitimate, that anginal pain represents a certain concentration of P factor (Lewis, Pickering and Rothschild, 1931) around the pain nerve-endings, it seems probable that a lesser degree of coronary disease produces a given degree of ischaemia in the hypertrophied heart of subjects with hypertension than in the smaller hearts of subjects with normal pressures. If this conclusion is extended, it is possible that a more diffuse coronary narrowing leading to a more diffuse ischaemia may be a factor in producing cardiac failure, and that a lesser degree of coronary disease is adequate to do so when the arterial pressure is high than when it is lower. The alternative is to suppose that cardiac failure is due to a weakening of cardiac muscle contraction arising from a more subtle, but probably biochemical cause. A final decision between these factors is impossible in the absence of a yardstick by which to judge. But even if it be allowed that coronary disease plays a part in the pathogenesis of heart failure in hypertension, it is difficult to accept it as wholly adequate in view of the reported cases in which it has been slight or absent.

THE FUNDUS OCULI IN HYPERTENSION

Disturbances of vision in subjects with hypertension may be due to () but are usually due to hæmorrhage into the retina or ; found in subjects with more severe hypertension, some cases totally destroy vision. The importance of the fundus oculi lies, however, in the information it gives as to the effects of hypertension. Here alone the small arteries and arterioles are visible to direct inspection. Here, too, appears the earliest clinical indication of the onset of the malignant phase, the picture described by Liebreich (1859) as albuminuric retinitis and more accurately named hypertensive neuro-retinopathy (Fishberg and Oppenheimer, 1930). In the following account the changes found in the retinal arteries will first be described, then the types of retinopathy and their anatomical basis. Finally, the vexed question of the causation of retinopathy will be considered.

The Signs of Organic Disease of the Retinal Arteries

Normal retinal arteries show varying degrees of tortuosity, a uniform calibre diminishing as the vessels branch, and a light reflex from the centre of the vessel which has also a uniform thickness; the arterial wall is transparent enough to allow the dark colour of the vein to show through at the arteriovenous crossing. Size can be judged from the following ratios: artery 1; vein 1.1 to 1.4; optic disc 11 to 17, the arteries measuring 0.088 mm. to 0.134 mm. near the disc (Duke-Elder, 1945). Thus the abnormalities seen in the retinal arteries are those affecting the small arteries and arterioles, which are open to inspection in the living subject in the retina alone. The following abnormalities are found:

(1) *Variations in Calibre* This is one of the earliest and most constant signs of organic disease. Traced from the disc outwards, the artery will show long or short stretches when its diameter decreases and then increases again. These irregularities are associated with intimal proliferation (Coats, 1913) or with thickening of media or adventitia. They are often attributed to vascular spasm; falsely since, as Foster Moore (1917) showed, and I have time and time again confirmed, these constrictions persist quite unchanged for days, weeks and even years. The constrictions that come and go, described by Mylius (1928) and by Wagener (1933), must be very rare. I have never seen them and, of my ophthalmological colleagues, only Juler (1949) has seen them by very prolonged search as rather slight phenomena in the eyes of some patients with pregnancy toxæmia.

(2) *Phenomena at the Arteriovenous Crossing.* When a normal artery crosses in front of a normal vein, the vein is visible through the artery, seems to preserve its same diameter throughout and pursues its usual course. In advanced disease of the arteries the vein is invisible through the artery and appears to taper to a blunt point on either side (Gunn, 1898); its course is deflected so that it crosses the artery at right angles to the course of the artery (Moore, 1917). These phenomena are not usually due to nipping of the vein, since the diameters of the vein proximal and distal to the arteriovenous crossing are the same. The changes are due to thickening of media and adventitia of the arterial wall and to involvement of the veins by the periarterial thickening at their point of contact. Since a blue cylinder is being viewed through an overlying, semi-opaque, colourless cylinder, the blue colour is invisible in the centres and becomes more fully visible as the edge of the arterial wall is reached. True nipping of the veins sometimes occurs, and particularly when the veins are engorged by increased intracranial pressure or by thrombosis proximally.

(3) *Alterations in the light reflex* are of four kinds.

Irregularity is often associated with irregular calibre of the blood column, but the irregularity may be finer and may be beaded. An increase in the brightness of the light reflex (copper-wire arteries) is due to thickening and hyaline degeneration of the media. When the light reflex is obtained from the entire vessel, it appears as a silver streak (silver-wire arteries), also due to hyaline degeneration of the media, and often to total obliteration of the blood column. Finally, the vessel may be sheathed with a brilliant white line which may simply appear at the sides of the vessel or cover it entirely. This is generally attributed to a fibrotic perivascularitis. That this sheathing does not occlude the artery is evident by the red colour reappearing distally.

(4) *Generalized reduction in calibre* is a fairly frequent phenomenon in retinal arterial disease. Gowers (1876) went so far as to say that it was proportional to the height of the pressure, but as he was unable to measure either, he was in a privileged position. Neame and I attempted to confirm this, measuring the arterial size with a graticule; but the results were difficult to interpret owing to the very inconstant number of branches of the retinal arteries. In general, it is agreed that narrow retinal arteries are common in patients with very severe hypertension, but they also occur in some old patients with normal pressures. This narrowing has been attributed to retinal arterial spasm; and it may well be a functional constriction. But in the case exhibiting the most severe narrowing I have seen, section of the optic nerve showed an acute arteriolar necrosis which nearly completely obliterated the lumen of the central artery of the retina; and Frieden-

wald (1933) has shown that intimal plaques in the central artery of the retina may also be the cause of vascular narrowing in old people.

The Question of Retinal Vascular Spasm

In another place (Pickering, 1951b) I have expressed strong views concerning the present tendency to invent "arterial spasm" as an explanation for phenomena that can be otherwise explained on a hypothesis that violates no cardinal principle of physiology. As one who was trained in physiological methods and to accept a standard of evidence that is general in experimental science, I find it hard to restrain myself over this question. Vasospasm and arterial spasm are terms that are very commonly applied to describe the two most conspicuous kinds of change seen in the retinal arteries, namely, the generalized and localized reductions in calibre. Now it is quite possible that the generalized narrowing of the retinal arteries which

... are almost certainly not due to this cause, since as all careful observers (Moore, 1917) have shown, they remain constant in position, and they are found, on histological examination, to correspond with localized thickening of the arterial wall. As has been mentioned, it is possible that occasionally small local contractions may come and go, but in spite of careful search for many years, I have still to witness this. This is not to deny that such contractions occur, for more expert ophthalmologists than I have seen them, but they have only seen them by very careful examination indeed in very few cases, and I contend, therefore, that they are uncommon and, in a general way, unimportant.

Finally, there are ...
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retinal arter
... not, however, peculiar to hyperten-
sion. Some of them have had mitral stenosis (e.g. Agatston, 1928). Others are now recognized as internal carotid thrombosis (Denny-Brown, 1951). There is reason to suppose, therefore, that the transient cessation of blood flow is due to an organic rather than a spastic cause. Such explanations do not, however, entirely account for ...
mena. I have ...
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flow on ...
... sight was regained in twenty minutes and on the subsequent day the retinal arteries appeared the same on the two sides. His internal carotid artery on the same side was normal and he had no mitral stenosis or auricular fibrillation. He

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FIG 12 4 Arteriosclerotic retinopathy, no papilloedema, "exudates" small and sharply defined. Lesion often unilateral. (After Foster Moore, *Quart J Med*, 1917, 10, 29)



FIG 12 5 Diabetic retinopathy, no papilloedema, no exudates, round red spots (microaneurysms) and blot hemorrhages (Dr Hansell)

(To face p 276.

had, however, intermittent claudication of some duration. In a man of this age, and with such a history, an organic cause is probable, even though it has not been identified.

TYPES OF RETINOPATHY AND THEIR RELATIONSHIP TO THE BENIGN AND MALIGNANT PHASES OF HYPERTENSION

Albuminuric retinitis was the term given by Liebreich (1859) to describe the retinal changes characteristic of an advanced stage of Bright's disease, and characterized by bilateral papilloedema, relatively large ill-defined white exudates, the so-called "cotton-wool" patches scattered over the retina but mostly near the disc, and a star figure or macular fan consisting of radiating irregular white lines or sheets grouped around the macula (Fig. 12.6). Linear and flame-shaped hæmorrhages grouped around the disc, and all grades of retinal arterial change, are common associated features. Volhard and Fahr (1914) recognized that the appearance of albuminuric retinitis was often the first sign heralding the change from the benign to the malignant course of essential hypertension. Later Volhard (1931) called this "retinitis angiospastica" to signify his view of its causation. Others called it renal retinitis.

In 1917 Foster Moore distinguished a second type of lesion which he termed arteriosclerotic retinitis (Fig. 12.4). This differed from the albuminuric form in being often unilateral, rarely associated with papilloedema, and characterized by small sharply defined glistening exudates, the diameter of a retinal vein or less; these were often grouped about the termination of small artery or vein, sometimes scattered irregularly over the fundus, and, when forming a macular fan, this consisted of discrete dots rather than lines or sheets. These dots often persisted unchanged for years, but were also observed to disappear slowly, leaving no trace. This retinal picture was always associated with signs of retinal arteriosclerosis, and was accompanied by a much better prognosis. It was common knowledge that patients with albuminuric retinitis rarely survived more than two years from its discovery. Of Foster Moore's cases of arteriosclerotic retinitis 10 females out of 17 were alive on an average three years and five months, and two males were alive two years and ten months after the onset of symptoms. Of the 17 patients who had died, seven died of cerebral hæmorrhage, while only two died of uræmia. Arteriosclerotic retinitis is, in fact, the type of retinitis, if any, found in the benign phase of hypertension. It seems to be the same lesion as "*leichte atypische Retinitis*" (Leber, 1915).

Albuminuric retinitis and arteriosclerotic retinitis, though they are the original terms by which these two types of retinal picture were distinguished are not entirely suitable terms because, amongst other

things, the reaction of the retina is not inflammatory. Fishberg and Oppenheimer (1930) therefore proposed the terms hypertensive neuro-retinopathy and arteriosclerotic retinopathy, which terms will hereafter be used.

It is to be emphasized that these two types of retinopathy are not utterly distinct, though they tend to be so. They form, as it were, two distribution curves with considerable overlap. It is generally agreed that the essential distinguishing feature is the presence of bilateral papilloedema in the hypertensive neuro-retinopathy.

A third type of retinopathy may be conveniently mentioned here, namely, diabetic retinopathy (Fig. 12.5). It was at one time disputed whether this was not the same as arteriosclerotic retinopathy, because there are many points in common. But it is now known (p. 360) that the basic pathology of the arteriosclerotic form is arterial, that of diabetic retinopathy, venous. In diabetic retinopathy, the earliest abnormalities are minute round red spots, once known as hæmorrhages, now known as venous microaneurysms; later, irregularly circular "blot" hæmorrhages occur and large soapy or waxy exudates. The condition is usually bilateral, but papilloedema is not a usual or essential component.

The first sign of hypertensive neuro-retinopathy may be swelling of the disc; more often, in my experience, a soft ill-defined exudate suddenly appears, or perhaps more than one. In some patients these exudates seem to come and go and the patient may succumb, or be treated successfully, before the full picture supervenes. In others there is a steady succession of exudates and hæmorrhages and progressive swelling of both discs. In following these exudates in one and the same patient I have been struck by the fact that they often appear to be

... which it was first seen, though it had not been there three days before; it had vanished completely seventeen days later. Others, smaller and more sharply defined, seen at the same time, remained quite unchanged in size or appearance over the three weeks they were observed.

Some authors have tried to subdivide hypertensive neuro-retinopathy into a number of varieties. Thus Duke-Elder (1945) gives: renal retinopathy, toxæmic retinopathy, and malignant hypertensive retinopathy. I agree with Volhard (1931) in being unable to distinguish ophthalmologically between these varieties, except (1) that signs of organic vascular change are commoner in older subjects and those with long-standing hypertension, than in younger subjects with more acute hypertension, such as subjects with nephritis and pregnancy toxæmia, and (2) that subjects with generalized œdema are more likely to show greater retinal œdema; its extreme form, retinal



FIG. 12.6



FIG. 12.7



FIG. 12.8

FIGS. 12.6-8 Hypertensive neuroretinopathy resolving after blood pressure reduced by excising a hydronephrotic pyelonephritic left kidney on February 25th, 1946. Paintings made: February 28th, 1946, May 3rd, 1946, August 20th, 1947. Case history on page 296

terized especially by exaggeration of the arterial reflex and arterio-venous compression, or of the postangiostatic type characterized especially by generalized and localized irregular narrowing of the arterioles." In Group III was found "retinitis of the angiostatic type, characterized especially by edema, cotton-wool patches, and hemorrhages in the retina superimposed on a combination of sclerotic and spastic lesions in the arterioles" "If measurable edema of the disks is added to this picture, the case belongs to Group IV."

This classification has served a useful purpose in directing attention to the importance of the fundus oculi in assessing the severity of the effects of hypertension. It is unacceptable for two reasons. In the first place, it propagates a myth that the localized narrowings of the retinal arteries are usually due to arterial spasm.¹ In the second place it does not clearly distinguish between the benign and malignant types of retinopathy.

Thus the clinical significance of a large, ill-defined exudate appearing in the fundus of a pregnant woman with specific hypertensive disease of pregnancy, or in a young man with a gross hypertension, is quite different from the presence of a collection of sharply defined glistening exudates in a person of 60 with a moderate hypertension. In neither type of retinal picture is papilloedema present. Both would be classified as Group III. But in the first instance the nature of the exudate and the circumstances under which it has appeared suggest the earliest stages of hypertensive neuro-retinopathy and the onset of the malignant phase of hypertension. In my view the exudate would imply the termination of pregnancy in the one case and the immediate use of drugs which lower blood pressure in the other; for it is too common an experience that to wait for the full picture of hypertensive neuro-retinopathy before instituting treatment may mean that irreparable harm has been done to the kidneys (see p. 228). In the second instance, however, the retinal picture is clearly that of arteriosclerotic retinopathy, characteristic of the *benign form*. Here energetic therapy may not be necessary, though, of course, should bilateral papilloedema later supervene, the retinopathy would then fall into the class of

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show different diagnostic and therapeutic implications. This will not

¹ If this were merely a hypothesis, I should have no objection to it. But it has become dogma, a dogma moreover that is quite opposed by the evidence.

detachment, is thus commoner in nephritis and in toxæmia of pregnancy than in other forms of hypertension.

Hypertensive neuro-retinopathy is, as has been said, the clinical "sine qua non" of the malignant phase of hypertension. It has been described, and I have personally observed it, in the following conditions: the malignant phase of essential hypertension, acute nephritis, chronic nephritis, chronic pyelonephritis, polycystic kidney, Cushing's syndrome, pheochromocytoma, polyarteritis nodosa, toxæmia of pregnancy, urinary obstruction due to stone (? with chronic pyelonephritis). It has also been described in lead poisoning. I have never observed it, and, as far as I know, it has never been described in coarctation of the aorta. In the absence of treatment the patients who display it are, with a single exception, suffering from a hypertension of such rapid course that they usually die within the year, and seldom survive more than two. The exception to this rule is provided by pregnancy toxæmia, where parturition usually lowers arterial pressure with the rapid disappearance of retinopathy. Very occasionally with persistent hypertension the retinitis subsides spontaneously; I have seen two such cases only in my entire experience; Keith and Wagener (1951), in the much more extensive practice of the Mayo Clinic, described fifteen.

Arteriosclerotic retinopathy may remain stable for years, or vanish without trace. Sharply defined exudates may be accompanied by undoubted swelling of a disc that remains unilateral and subsequently disappears; in one of my cases it was followed by optic atrophy and by very conspicuous sheathing of the retinal arteries leaving the disc (e.g. Case 29, Pickering, 1934). Not infrequently, however, sharply defined exudates are followed by bilateral papilloedema and the condition passes from the category of arterio-sclerotic retinopathy into that of hypertensive neuro-retinopathy (e.g. Case 9, Pickering, 1934).

Arteriosclerotic retinopathy usually occurs in older subjects, of whom the vast majority have essential hypertension that is still in the benign phase. I have seen it, however, also in chronic nephritis, chronic pyelonephritis and polycystic kidney.

The Classification of Keith, Wagener and Barker (1939)

The classification of the fundus changes suggested by these workers has been widely used, but is not acceptable by me. They divided the fundus lesions into four groups of increasing severity and showed that expectation of life was closely related to the fundus changes (Table 14.8, Chapter 14). In Group I the retinal vessels showed only mild narrowing or sclerosis. In Group II, the retinal arteries showed moderate to marked sclerosis "whether of the chronic type, charac-

minuric retinitis was always associated with hypertension; further, that it was characteristic of that category of hypertension which he called "pale" hypertension, in which he considered a vasoconstrictor substance of renal origin was present in the circulating blood. Impressed by the narrowing of the retinal arteries, he considered the retinal lesions were ischemic in origin due to retinal arterial spasm, and he designated the condition "retinitis angiospastica." This view has been widely held since and the important papers of Keith and Wagener (1939, 1951) employ the term "vasospastic retinitis." The evidence for retinal arterial spasm has been discussed, and the conclusion reached that while generalized narrowing of the retinal arteries may represent vaso-constriction, localized constrictions are almost always organic. Volhard attributed the neuro-retinopathy to generalized ischemia of the retina. I find this difficult to accept since the retina is very sensitive to deficiency of blood supply, and these patients get no greater visual disturbances than do patients with brain tumour with retinal lesions of similar extent and degree. Nevertheless, I have seen a very similar retinal picture develop after severe gastrointestinal hæmorrhage.

In considering this problem it is important that we should bear in mind that there are two types of retinopathy in hypertension, in one of which bilateral papilloedema is present, in the other of which it is absent. Arteriosclerotic retinopathy is, in fact, characterized by focal lesions of the retina only. These lesions are always associated with ophthalmoscopic signs of organic disease of the retinal arteries. Thus and the nature of the histological changes in the retina suggest that the white spots are in fact minute infarcts of the retina, closely resembling the minute infarcts also found in the brain and, like them, due to narrowing or closure by intimal thickening of the smaller arteries and arterioles. Some of the exudates in *non-arteriosclerotic* may be of similar origin, that is is most likely to be due to *org*

published two cases of albuminuric retinitis in which he could find no organic changes in the retinal arteries, but his evidence was criticised by Verwey (1927) because he did not stain his arteries for fat. Verwey was able to demonstrate a hyaline lipid degeneration of the walls of the terminal arterioles of the retina in all cases of albuminuric retinitis examined. This work was confirmed by Friedenwald (1935), who was "convinced that albuminuric retinitis is in essence a complication of retinal arteriolar sclerosis"—"By studying the retina mounted as a whole . . . it was possible to show that the hyalinized arterioles were directly connected with the areas of 'cotton-wool spots.' In this way it was learned that those cotton wool spots which represented actual tissue necrosis and which on histological section show the peculiar

be done if we call them Types III and IV distinguished only by papilloedema. It may be done if we call them arteriosclerotic retinopathy and hypertensive neuro-retinopathy, having the characteristics already listed.

ANATOMICAL BASIS OF RETINOPATHY

Papilloedema. In their classical paper on the Pathology of Papilloedema, Paton and Holmes (1911), showed that the swelling of the disc seen in tumour of the brain was a true oedema of the nerve head which might extend into the folds of the surrounding retina occasionally producing a macular fan, and was accompanied by congestion of the smaller veins and capillaries in the disc itself. They attributed these changes to a rise in intracranial pressure extending along the sheath of the optic nerve and so raising the pressure in the central retinal vein and hindering the lymph drainage from the retina. In the single case of albuminuric retinitis, examined by Paton and Holmes, the changes in the nerve-head were similar, but they found, of course, the diffuse changes in the arteries, even to complete obliteration of the intima, and the lesions of the retina, both of which were absent in tumour of the brain. Bordley and Cushing (1909) compared sections of the retina from patients dying of brain tumour and chronic nephritis and concluded that the histological picture varied but little in the two conditions and the essential features of each left little doubt as to their close histological connection. From some accounts it appears that the oedema fluid in hypertensive neuro-retinopathy is more fibrinous than in tumour of the brain, but the writer knows of no other large scale comparison between the histology of the two.

Exudates. The composition of the exudates varies greatly. Some of the fresh cotton-wool patches are local collections of fibrin-containing oedema. The older and harder exudates and especially those forming the macular star figure, are collections of hyaline and lipoid droplets either alone or in the phagocytic cells. To quote Duke-Elder (1945): "The white patches seen ophthalmoscopically may therefore have a varying pathological constitution; they may represent areas of oedema, masses of fibrin, absorbing hæmorrhages, varicose nerve-fibres forming cytoïd bodies, fatty deposits, islands of necrosis or of hyaline accumulations."

THE PATHOGENESIS OF THE RETINAL LESIONS

For many years it was believed that albuminuric retinitis was due to "toxins" produced or retained by the diseased kidney. Although this view is still presented in some current textbooks of ophthalmology, it has no foundation of evidence (Volhard, 1931; Fishberg, 1939), and will not be further considered. Volhard pointed out that albu-

minuric retinitis was always as that it was characteristic of the called "pale" hypertension, in substance of renal origin was present in the circulating blood. Impressed by the narrowing of the retinal arteries, he considered the retinal lesions were ischaemic in origin due to retinal arterial spasm, and he designated the condition "retinitis angiospastica." This view has been widely held since and the important papers of Keith and Wagener (1939, 1951) employ the term "vasospastic retinitis." The evidence for retinal arterial spasm has been discussed, and the conclusion reached that while generalized narrowing of the retinal arteries may represent vaso-constriction, localized constrictions are almost always organic. Volhard attributed the neuro-retinopathy to generalized ischaemia of the retina. I find this difficult to accept since the retina is very sensitive to deficiency of blood supply, and these patients get no greater visual disturbances than do patients with brain tumour with retinal lesions of similar extent and degree. Nevertheless, I have seen a very similar retinal picture develop after severe gastrointestinal haemorrhage.

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retinal ar . . . mounting the retina mounted as a whole . . . it was possible to show that the hyalinized arterioles were directly connected with the areas of 'cotton-wool spots.' In this way it was learned that those cotton wool spots which represented actual tissue necrosis and which on histological section show the peculiar

cytoid bodies, are, in fact, minute infarcts due to arteriolar occlusion " (Friedenwald, 1933).

If the focal ischæmia is the whole or part explanation of the focal retinal changes or exudates, what is the cause of the papilloedema and of the more diffuse œdema of the retina which is the essential and distinct feature of hypertensive neuro-retinopathy, distinguishing, in fact, the benign from the malignant phase of hypertension? Is the papilloedema due to the same disturbance as in most other diseases in which it occurs, namely, to raised intracranial pressure? The view that it is was put forward in 1908 by Cushing and Bordley, who cited in evidence the improvement in the retinal condition witnessed after repeated lumbar puncture, and the complete regression of retinitis in one case of their own and one of Bramwell's, in which an operation for cerebral decompression was performed. But in one of the cases improving after lumbar puncture and in one of the two that were decompressed, the condition followed pregnancy, under which condition the lesions are frequently transient. In Grant's (1932) two cases, decompressed because of the mistaken diagnosis of cerebral tumour, the retinitis failed to improve, but neither did the raised intracranial pressure fall. This evidence then is quite inconclusive. So far as c.s.f. pressure is concerned, Quincke (1910) noted the presence of a raised pressure in 18 cases of nephritis in uræmia. Larsson (1924) described 11 cases of nephritis with neuro-retinitis, in all of which the lumbar pressure was raised. McAlpine (1932) described three cases with neuro-retinitis and raised intracranial pressure. Larger series were published by Shelburne, Blain and O'Hare (1932), and by me (Pickering, 1934). Shelburne, Blain and O'Hare found that 19 of 20 patients with c.s.f. pressures exceeding 200 mm. H_2O had papilloedema, while this lesion was present in only two of 30 patients with lower pressure. All my patients with pressures over 250 mm. H_2O , either had, or subsequently developed, hypertensive neuro-retinopathy; while of those with lower pressures one had hypertensive neuro-retinopathy, eight had arteriosclerotic retinopathy and 12 had no lesions of the retina apart from arteriosclerosis. I therefore suggested that the difference between hypertensive neuro-retinopathy and arteriosclerotic retinopathy was the presence of neuro-retinal œdema in the former and its absence in the latter, and that this was dependent on the level of c.s.f. pressure. Fishberg (1939) wrote that he had "found the cerebrospinal pressure elevated in all instances of hypertensive neuro-retinopathy in which papilledema was well marked and often also when it was but slight. But I have repeatedly observed normal pressure of the cerebrospinal fluid in hypertensive neuro-retinopathy at a time when there was little or no edema of the disk even though the retinal lesions were very severe." Many other workers have been impressed with the frequency with

which normal c.s.f. pressures are associated with neuro-retinopathy. Hetzel (1951) found c.s.f. pressures of under 180 in seven, 180 to 240 in seven, and 245 to 500 in six. Taylor, Corcoran and Page (1954) found that "13 per cent. of patients with hypertension but without papilloedema had abnormally elevated CSFP; many patients with papilloedema did not show elevated CSFP, and in those whose papilloedema fluctuated, remitted, or recurred, no association could be demonstrated between these changes and the level of CSFP." The evidence then is highly controversial. I am naturally prejudiced in favour of my own measurements, which I made myself. I know how easily loss of fluid and faulty posture may interfere with pressure measurements made by interns, as most of these series appear to have been. Nevertheless, I do agree with others that even when all precautions are taken, there are some cases with neuro-retinopathy in which the c.s.f. pressure is not high.

However, the evidence for the rôle of raised intracranial pressure is about as impressive in hypertensive neuro-retinopathy as it is for papilloedema in cerebral tumour. Thus in Ayer's (1929) series of 61 patients with cerebral tumour, 42 had c.s.f. pressures above 250 mm. H_2O , and of these 39 had papilloedema and three had not; 10 had lower c.s.f. pressures and of these six had papilloedema and 4 had not.

In my series of patients with hypertension, I was unable to find any consistent elevation of c.s.f. pressure during the presence of headache or the coma following hypertensive fits, as compared with the pressure in the same patient when these features were absent. Only one factor correlated with c.s.f. pressure, namely, diastolic arterial pressure, it therefore seemed that the distinctive features of the retinal lesion of the malignant phase of hypertension were due to the level of

$r = 0.906$ (highly significant) and $r = 0.346$ (not significant) respectively. Taylor, Corcoran and Page observed no correlation between c.s.f. pressure and diastolic blood pressure in benign hypertension but a low correlation ($r = 0.271$).

Figs 12.6, 12.7 and 12.8

patient with malignant hypertension whose arterial pressure was reduced permanently by excising a hydronephrotic pyelonephritic kidney. The papilloedema and large soft exudates had disappeared entirely after two months, the star figure was then unchanged (Fig. 12.7) but had gone after seventeen months (Fig. 12.8). These changes

cytoid bodies, are, in fact, minute infarcts due to arteriolar occlusion" (Friedenwald, 1933).

If the focal ischaemia is the whole or part explanation of the focal retinal changes or exudates, what is the cause of the papilloedema and of the more diffuse oedema of the retina which is the essential and distinct feature of hypertensive neuro-retinopathy, distinguishing, in fact, the benign from the malignant phase of hypertension? Is the papilloedema due to the same disturbance as in most other diseases in which it occurs, namely, to raised intracranial pressure? The view that it is was put forward in 1908 by Cushing and Bordley, who cited in evidence the improvement in the retinal condition witnessed after repeated lumbar puncture, and the complete regression of retinitis in one case of their own and one of Bramwell's, in which an operation for cerebral decompression was performed. But in one of the cases improving after lumbar puncture and in one of the two that were decompressed, the condition followed pregnancy, under which condition the lesions are frequently transient. In Grant's (1932) two cases, decompressed because of the mistaken diagnosis of cerebral tumour, the retinitis failed to improve, but neither did the raised intracranial pressure fall. This evidence then is quite inconclusive. So far as c.s.f. pressure is concerned, Quinke (1910) noted the presence of a raised pressure in 18 cases of nephritis in uraemia. Larsson (1924) described 11 cases of nephritis with neuro-retinitis, in all of which the lumbar pressure was raised. McAlpine (1932) described three cases with neuro-retinitis and raised intracranial pressure. Larger series were published by Shelburne, Blain and O'Hare (1932), and by me (Pickering, 1934). Shelburne, Blain and O'Hare found that 19 of 20 patients with c.s.f. pressures exceeding 200 mm. H_2O had papilloedema, while this lesion was present in only two of 30 patients with lower pressure. All my patients with pressures over 250 mm. H_2O , either had, or subsequently developed, hypertensive neuro-retinopathy, while of those with lower pressures one had hypertensive neuro-retinopathy, eight had arteriosclerotic retinopathy and 12 had no lesions of the retina apart from arteriosclerosis. I therefore suggested that the difference between hypertensive neuro-retinopathy and arteriosclerotic retinopathy was the presence of neuro-retinal oedema in the former and its absence in the latter, and that this was dependent on the level of c.s.f. pressure. Fishberg (1939) wrote that he had "found the cerebrospinal pressure elevated in all instances of hypertensive neuro-retinopathy in which papilledema was well marked and often also when it was but slight. But I have repeatedly observed normal pressure of the cerebrospinal fluid in hypertensive neuro-retinopathy at a time when there was little or no oedema of the disk even though the retinal lesions were very severe." Many other workers have been impressed with the frequency with

most intense and severe in the kidney. Provided the patient has not died of cerebral hemorrhage or left ventricular failure at an early stage, the kidney is thus always involved in the malignant phase; and it is the course of the renal lesion that dominates the course of the disease.

The relationship between the onset of the retinal and the renal lesion in the malignant phase of essential hypertension is very variable. In a few patients the retinal lesion may exist for a considerable time before the kidneys are affected. In 68 patients in whom the diagnosis of malignant nephrosclerosis was established at autopsy, papilloedema was absent in 16, or 23 per cent. (Goldring and Chasis, 1944). But in most the two seem to begin more or less together. The first sign of renal involvement is usually the sudden appearance of marked proteinuria. In about 20 per cent. of patients gross painless hæmaturia indicates the occurrence of necrosis of the renal arterioles; in about 50 per cent. persistent microscopic hæmaturia has the same significance. But the absence of hæmaturia does not imply the absence of necroses (Goldring and Chasis, 1944).

From these first signs the renal lesion may progress slowly over a period of a year or even more, or it may progress exceedingly rapidly to fatal uræmia in a few weeks. In the more slowly progressive lesions, the functional tests gradually decline, polyuria supervenes, the concentration of urea and other urinary constituents in the blood rises, and eventually the patient presents the familiar picture of uræmia with vomiting, drowsiness, hyperpnœa, hæmorrhages into the skin and bowel and finally, coma and death.

OTHER ORGANS AND TISSUES IN HYPERTENSION

For a comprehensive view of the function of other organs in hypertension, the reader is referred to Fishberg's book (1939). In brief the alimentary canal and its associated organs, the heart, the lungs, the liver, show no obvious evidence for abnormal

arterial pressures

are not higher as in subjects with

It is probable that the manifestations

are not a survey of this point.

are quite consistent with the large exudates here seen, being collections of oedema fluid. The star figure was obviously of different composition. It is generally believed to be due to the collection of fibrinous exudates forming the radial pattern, because of the anatomical arrangement of the attachments between the various layers of the retina at this point. Presumably in this case the star figure was composed of lipid.

THE KIDNEY IN ESSENTIAL HYPERTENSION

The behaviour of the kidney in essential hypertension is very closely related to the vascular lesions in it ; for the organic affections of small arteries and arterioles are, as was seen in Chapter 11, most widespread and intense in the kidney.

In the benign phase of essential hypertension, renal function, as tested by the older methods such as concentration and dilution, urea clearance, urea concentration and blood urea, usually remains within the limits accepted as normal. More detailed investigation reveals, however, that even the maximum specific gravity attained by the urine tends to be less in patients with essential hypertension than in normal subjects (Corcoran and Page, 1942b). The finer methods, such as inulin and diodone clearance reveal that, while the glomerular filtration rate may be normal, the diodone clearance is reduced, giving a higher filtration fraction. These changes have, as we have seen (Chapter 7) been variously interpreted as signifying contraction of the efferent and afferent glomerular arterioles. In severe and long-standing cases in which there is extensive elastosis in the interlobular and arcuate arteries, or extensive fatty hyaline intimal thickening of the arterioles, glomerular filtration rate is reduced, and the excretion of diodone even more so. However, in the benign phase of essential hypertension these changes are rarely sufficiently severe to produce urea retention unless there is a secondary cause such as heart failure. *Uræmia is exceedingly rare in the benign phase, but may occur as a result of a very slowly progressing renal failure due to the arterial lesions mentioned. But in general it may be said that the onset of uræmia should raise grave doubt as to the diagnosis of benign essential hypertension ; it is more probably secondary or malignant.*

Abnormal constituents of the urine are not found in most cases of benign essential hypertension. Protein and a slight excess of granular casts may occur in the severer cases, or those with cardiac failure. A considerable excess of red cells or white cells is, in general, evidence against benign essential hypertension.

While the kidney is thus very largely spared in benign hypertension, it bears the chief brunt of the disease in the malignant phase, for the characteristic lesion of the malignant phase, the arteriolar necrosis, is

except in relation to age. Another cause for variability in course is the multiplicity of types of vascular change, most of which appear to be only partly dependent on raised arterial pressure, and most of which are unrecognizable until disaster has occurred. Thus atheroma and its related intimal fibrosis are the lesions responsible for myocardial infarction and angina pectoris, for most cases of cerebral thrombosis and for intermittent claudication (whose relationship to raised arterial pressure is quite obscure). Medial degenerations are responsible for dissecting aneurysm of the aorta, and for aneurysmal dilatations of the abdominal aorta, possibly also for cerebral hæmorrhage. Elastosis of the medium sized arteries and fatty hyaline thickening of arterioles are probably responsible for some at least of the little strokes, and for the slow decline of renal function that sometimes occurs in the benign phase.

By contrast, malignant hypertension is strikingly uniform both in the pattern of disturbances presented, and in the length of time over which the drama is enacted. Such uniformity is usually associated in biology with a fairly well-defined causal sequence, and it is our present thesis, to be further examined in the next chapter, that once the arterial pressure has passed a given threshold, which varies somewhat from individual to individual, arteriolar necroses occur and it is the progressive development of these lesions that determines the course of malignant hypertension.

The course of malignant hypertension may be illustrated by data from Schottstaedt and Sokolow (1953), who studied 104 cases of whom, however, 40 per cent had pyelonephritis, 20 per cent glomerulonephritis and 40 per cent malignant nephrosclerosis. Those authors also included four patients with unilateral papilloedema, in two of whom the papilloedema was transient. I would not include these; hypertensive neuro-retinopathy is a bilateral affection as Foster Moore so clearly emphasized. The average age at diagnosis was 43 years. The average survival in 86 patients was 8.4 months; the range was from one day to seven years, with only six living more than two years and 50 dying within three months. Thirty patients had retinopathy. Thirty patients had hypertension, in 74 it was diagnosed five months to twenty-seven years earlier. The symptoms at onset are summarized in Table 12.9. The heart was enlarged clinically in 81, radiologically in 57. Symptoms of cardiac failure were present in 73, signs in 51; of these, signs of cardiac failure preceded the onset of the malignant phase in eight, coincided with it in 11, and occurred during the first year in 28 and the second year in four. Electrocardiogram showed left ventricular hypertrophy in 74, left bundle branch block in 11, right bundle branch block in 11, and normal in 8. The electrocardiogram was not done in 11 patients. The electrocardiogram was not done in 11 patients.

SUMMARY OF THE BENIGN AND MALIGNANT COURSES OF ESSENTIAL HYPERTENSION

As first used by Volhard and Fahr, the terms benign and malignant describe the course of hypertension. In the benign form, the condition is stable, there being often little change from year to year and death, when it comes at length, is due to heart failure, apoplexy or intercurrent disease. In the malignant form the condition rapidly deteriorates, with progressive renal failure predominating, and death comes, often within the year, of uræmia, left ventricular failure or cerebral hæmorrhage. Clinically, the two forms are most clearly separated by the appearances of the fundus oculi, the malignant phase showing the large, ill-defined exudates, and ultimately the bilateral papilloedema of hypertensive neuro-retinopathy; the benign phase usually shows no retinal lesion other than vascular, or it may show the lesions of arteriosclerotic retinopathy, the exudates being small and sharp, and papilloedema being absent or, rarely, unilateral and transient. The two courses are, as we have seen, expressive of the arterial lesions. In the benign form the most important arterial lesions are atheroma and fatty hyaline thickening of the arterioles, both lesions being intimal and both slowly progressive. In the malignant form the characteristic lesion is the arteriolar necrosis, a lesion that can develop very quickly, affect all coats of the vessel, particularly the media, and rapidly produce ischæmia; this lesion is found especially in the kidney.

Of these two forms of essential hypertension, the benign form is a much less clearly defined entity and presents much variation, both in the nature of the chief incidents of the disease, and in the length of time that elapses between the first and the last. The rather distant relationship between arterial pressure and morbidity is shown by the facts that one-third of the patients, labelled as having essential hypertension, die of something unconnected with it, and about a half die of heart failure whose relationship to raised blood pressure is not fully understood.

Attempts to classify patients with benign hypertension into groups whose clinical courses are sufficiently well defined to form some guide to prognosis will be considered in Chapter 14.

Some of the variability in the course of benign essential hypertension is undoubtedly due to differences in blood pressure level. All hitherto published reports on the course of benign essential hypertension accept some arbitrary division between normal and abnormal, the divisions being distributed on both sides of 150/100. As was clearly shown in previous chapters, arterial pressure behaves as a graded characteristic and departures from the norm cannot be legitimately considered

suggestive of chronic pyelonephritis. A past history of generalized oedema or of hæmaturia following infection favours chronic nephritis. The rarer causes such as polycystic kidney, Cushing's Syndrome and polyarteritis nodosa have unmistakable features which will be described in the relevant chapters.

SUMMARY

A summary of this chapter can be no more than a guide to its contents, since it is largely concerned with clinical detail. Since

its early stage is obscure. Its later stage may follow the benign or malignant course. The benign course is relatively stable; its chief complications are cardiac and cerebral. Cerebral vascular disease is almost entirely to be ascribed to organic arterial lesions, in the production of which age and arterial pressure are two important factors, but not the only two. Cardiac failure is partly to be ascribed to cardiac load, and partly to vascular disease; but it is not certain whether these together with age entirely account for it. In other cases of benign hypertension, rarer manifestations of medial and intimal vascular disease, such as dissecting aneurysm (of the thoracic aorta) and arteriosclerotic aneurysm of the abdominal aorta may occur. In yet others, those diseases which normally afflict an ageing population may be the cause of death. By contrast the malignant course is much more rapid and more uniform in its features. It is heralded by hypertensive neuro-retinopathy, if at that time renal function is not impaired, and it usually is, it soon declines, often very rapidly; and the patient dies of uræmia often within the year, sometimes in a few months and very rarely survives several years. Left ventricular failure and cerebral vascular accidents are common and may carry off the patient before the terminal uræmia.

occurred in 88 per cent., but was not characteristic, and preceded the malignant phase in one-half. Cerebrovascular disturbances occurred in 44 patients of whom 25 had strokes. Convulsions occurred in 18, two-thirds of whom were in terminal uræmia. Thirty-seven patients had satisfactory renal function in the presence of papilloedema when seen initially. In this group the average survival of untreated patients was 16.3 months. Impairment of renal function developed in as short a time as one week and uræmia developed in one month in one patient. Three other patients developed uræmia within two months, and nine became uræmic in six months or less. The rapidity with which the kidney may be destroyed in malignant hypertension is a lesson which I have also learned many times, and makes the treatment of malignant

TABLE 12.9. *Symptoms marking Onset of Malignant Phase in 104 Cases (Schottstaedt and Sokolow, 1953).*

Visual impairment	79
Acute headache	6
Gross hæmaturia	5
Visual impairment and hæmaturia	3
Acute cardiac failure	1
Nausea, vomiting and epigastric pain	1
Undetermined owing to vagueness of symptoms	0

hypertension as much a matter of urgency as that of cancer or of a septicæmia.

In the final stages of malignant hypertension the patient usually displays the phenomenon of renal failure or uræmia (see p. 262) particularly nausea and vomiting; he is pale and anæmic; heart failure of the congestive or left ventricular type, pulsus alternans and gallop rhythm are common; one or more major or minor cerebrovascular accidents may have occurred; headaches are frequent and severe, and the patient is nearly blind from neuro-retinopathy. This tragic picture is the end stage not only of malignant essential hypertension, but also of chronic nephritis, chronic pyelonephritis, and more rarely of other types of hypertension. The differentiation of the malignant phase of essential hypertension from the end stages of chronic pyelonephritis and chronic nephritis can often only be made with certainty when the patient with malignant essential hypertension presents with papilloedema and normal renal function. When, as is at least as common, the renal lesion has already begun, the differentiation is more difficult; a past history of urinary infection, the presence of a stone or anatomical abnormality of the kidney, and the demonstration of bacteria and a gross excess of leucocytes in the urine are strongly

sympathectomy for hypertension, the average pressures in their groups 1 to 4 were respectively 191/115, 217/131, 225/134 and 227/148, the first three groups representing increasing grades of severity of benign hypertension and group 4 malignant hypertension. Similarly in Bechgaard and Hammarström's (1950) series, the incidence of high systolic and diastolic pressures was greatest in the malignant group. Nevertheless, all observers are agreed that there are exceptions to the general rule. It is not uncommon to have a patient whose diastolic pressure is recorded as over 140 mm. Hg for many years without hypertensive neuro-retinopathy or renal impairment developing. On the other hand, hypertensive neuro-retinopathy and arteriolar necroses may develop in patients who have persistently had lower pressures, especially in those whose hypertension is of recent origin.

These anomalies may have a variety of explanations. In Chapters 2 and 3 we saw how imperfect an appreciation we obtain of the pressure in the aorta during the ordinary conditions of life by indirect estimations made on the arm in the clinic. Again, it is common knowledge that in any heterogeneous biological population a given stimulus produces a range of response scattered on both sides of a mean. Some of the anomalies may thus represent no more than the effects of ordinary biological variation. There is, however, the strong suggestion, both from experimental work and the clinic, that the phenomena of the malignant phase occur at a lower pressure when the rise is recent, than when it is remote and, therefore, that not only the level but the rate of rise of arterial pressure are determining factors. Thus in his follow up of 1,000 cases of hypertension at ten and twenty years, Bechgaard (1954) found that 13 had entered the malignant phase in the first ten years, but no further cases in the second ten years. Thus it seems that the influence of arterial pressure may be modified by other factors. What these other factors are is quite uncertain. It may be suggested that the commoner lesions in

protects - such as raised arterial pressure, just as the arterioles in the kidney may be protected by a clamp on the renal artery. Again some associated disturbance like anaemia, which is common in nephritis and eclampsia, the chief kinds of recent hypertension, may produce vasodilatation and thus unduly expose the vulnerable vessels to the head of arterial pressure. The only evidence which I know suggesting the last possibility is the occurrence in patients, after severe hæmatemesis and melæna, of retinal lesions not unlike those of hypertensive neuro-retinopathy.

The hypothesis here presented is also in agreement with observations

CHAPTER 13

THE BENIGN AND MALIGNANT PHASES OF HYPERTENSION

THE NATURE OF THE MALIGNANT PHASE

IN the last chapter it was pointed out that essential hypertension may follow the benign course with wide variation in the lesions displayed, and in their progression, or it may follow the malignant course, a much more uniform picture characterized by a specific type of retinal lesion, hypertensive neuro-retinopathy, by progressive renal failure, and by the presence of acute arteriolar necroses, predominantly in the kidney, but occurring also in gut, pancreas, adrenal, heart, brain and eye. In Chapter 5 was described the experimental evidence suggesting that these acute arteriolar necroses were chiefly an expression of a grossly raised intra-arterial pressure, and perhaps of the speed at which this raised pressure developed. In Chapter 11 it was seen that the evidence in man was broadly consistent with this conclusion. In the last chapter the evidence was described which led to the supposition that bilateral papilloedema, the specific feature of the retinopathy of malignant hypertension, was chiefly a consequence of the level of intracranial pressure, which was in its turn partly determined by the diastolic arterial pressure. In view of subsequent work, this latter conclusion cannot now be taken as established, though I would say in its defence that it was not a hypothesis from which work began, but rather one which emerged from data collected with some modest care. Nevertheless, these concepts regarding the obligatory pathological and clinical features of malignant hypertension were important in suggesting that the syndrome of malignant hypertension was essentially an expression of a very severe hypertension. Conversely, if the arterial pressure did not rise sufficiently high for sufficiently long, neither hypertensive neuro-retinopathy nor arteriolar necroses developed, and the clinical course conformed to the benign type.

This concept of the nature of the benign and malignant courses was broadly in agreement with the levels of arterial pressure observed. Thus Volhard (1931) noted that the diastolic pressure was usually higher in malignant than benign hypertension. Page (1939b) and Ellis (1938) agreed that in the malignant phase the pressure was rarely under 130 mm. Hg. In Woods and Peet's (1941) patients who had undergone

arterial pulse. Pale hypertension, which included renal hypertension and the malignant phase of essential hypertension, was due to active constriction of the small arteries and arterioles by a chemical substance which he believed to arise from the kidneys as a result of ischaemia. He supposed that when, in red hypertension, the pre-arterioles contracted sufficiently, in response to the distending pressure to reduce renal blood flow below a certain level, a renal pressor substance was released and the active vasoconstriction of pale hypertension added; this change in the mechanism of hypertension was reflected clinically in the change from benign to malignant hypertension. He believed further that the distinctive clinical and pathological features of malignant hypertension, albuminuric retinitis, acute necrosis and intimal thickening of the arterioles, were likewise results of local ischaemia consequent on the intense vasoconstriction caused by the circulating pressor substance. Thus he believed that the development of pale hypertension led to a vicious circle, renal ischaemia leading to a release of a renal pressor substance, which produced a further renal ischaemia with intensification of the hypertension.

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Thus the close similarities between the terminal stages of chronic nephritis and the malignant phase of essential hypertension were so striking as to lead British workers to misname the latter chronic interstitial nephritis and Volhard and Fahr "die Kombinationsform". Even now it is impossible to establish with certainty during life whether a patient in his 40's, presenting with hypertensive neuro-retinopathy, gross hypertension and renal failure is in the terminal stage of chronic nephritis or malignant essential hypertension, unless he gives a past history of nephritis. The size of the terminal organs is by the finding of acute arteriosclerosis in the terminal organs of undoubted cases of nephritis.

Klemperer and Otani (1931), and Wilson and Altschule (1935). These acute necroses must add to the rate and extent of renal destruction as Wilson and Byrom (1939, 1941) pointed out.

While it is clear that in nephritis a phase is common, presenting every feature that distinguishes the malignant from the benign phase of essential hypertension, a phase corresponding to the benign form is less common and less well recognized. It is commoner in the benign form than in the malignant form.

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Again, if the benign and malignant courses are merely expressions of differences in the degree of hypertension, it would be expected that the division between them would not be absolute, and that in certain patients whose pressures are close to the threshold level, the characteristic features of malignant hypertension would come and go. This is most easily seen in the fundus oculi, where it is not uncommon for exudates that are too large and too ill-defined for the arteriosclerotic form to come and go before the accession of bilateral papilloedema completes the picture of *neuro-retinopathy*. That the retinal picture of malignant hypertension may occasionally revert to that of the benign form has been shown by Keith and Wagener (1951).

Thus the hypothesis is, broadly speaking, in conformity with the facts gleaned from a study of essential hypertension. Here, however, we are more particularly concerned with the broader implications of the hypothesis. One of the classical methods of testing a hypothesis is to make deductions from it and see if these deductions are true. The hypothesis just developed enables two predictions to be made. The first is that if the benign and malignant phases are merely expressive of the severity of the hypertension, then these same two phases, first distinguished in essential hypertension, should be found in other types of hypertension due to other and specific lesions; provided always, on the one hand, that these lesions are not themselves too rapidly progressive to enable a long continued hypertension of the benign type to be displayed and, on the other, that the hypertension should, in some cases, reach a degree consonant with the malignant phase. The second prediction is that if treatment enables the arterial pressure to be reduced sufficiently and for long enough, the hypertension should revert from the malignant to the benign phase. These two possibilities will now be examined.

THE MALIGNANT PHASE IN TYPES OF HYPERTENSION OTHER THAN ESSENTIAL

Volhard and Fahr (1914) at first regarded the malignant form as due to the superimposition of an exogenous nephritis on an endogenous hypertension. Later Fahr (1919), the pathologist, discovered the importance of arteriolar necroses which he attributed to toxins such as those of syphilis, lead and articular rheumatism. Volhard (1931), the clinician, noticed the similarities between nephritic, and other forms of severe hypertension, and malignant hypertension, and developed his concept of red and pale hypertension. Red hypertension, which corresponded to the benign phase, was, he thought, due to the effects of age on a certain genetic constitution; the hypertension was due to elastosis of the pre-arterioles which became less distensible by the

Nephritis is not, however, the only disease that may present the characteristic features of the malignant phase. In 1929 Ask-Upmark described six cases of malignant hypertension in adolescents in which was found a peculiar renal lesion characterized by unilateral hypoplasia, and an enlarged and deformed renal pelvis having one or more recesses ending blindly near the surface of the kidney. These kidneys probably were affected by pyelonephritis, to the clinical importance of which, and its relationship to malignant hypertension, attention was first drawn by Longcope (1937). In Weiss and Parker's (1939) experience at the Boston City Hospital, 15 to 20 per cent. of patients dying of malignant hypertension had chronic pyelonephritis; in Schottstaedt and Sokolow's (1953) series the figure was 40 per cent. In pyelonephritis also the hypertension may be stable and conform to the benign form.

In 1934 MacMahon, Close and Hass described two cases of Cushing's syndrome in which the post-mortem findings were those of malignant hypertension. More usually in Cushing's syndrome the hypertension is of the benign form. In 1935 MacMahon and Pratt, reviewing malignant nephrosclerosis, concluded that it was not merely a progression of benign sclerosis, but a distinct and separate disease that might exist alone, or complicate benign sclerosis. They considered that the etiology of benign and malignant hypertension had much in common since they might both occur in lead poisoning, pituitary basophilism and toxemias of pregnancy. Derow and Altschule (1935) described a series of cases and, after reviewing previous writings, concluded that malignant hypertension "is a syndrome which may occur: (a) with no evidence of previously existing hypertension; (b) as the end stage of essential hypertension . . .; (c) as the end stage of a miscellaneous group of conditions characterized by hypertension secondary to acute, sub-acute or chronic glomerular nephritis, pyelonephritis, adrenal tumor, pituitary basophilism, periarteritis nodosa, hyperemesis gravidarum, chronic lead poisoning, etc." They repeated this suggestion in 1941 and stated that "the mechanism by which the benign course of primary or secondary hypertension is suddenly and dramatically transformed into the rapid, progressive, downhill course of the syndrome of malignant hypertension is not understood." The hypothesis here presented provides an explanation of what the mechanism might be. I would amend Derow and Altschule's list by substituting pregnancy toxemia for hyperemesis gravidarum and adding polycystic kidney. In fact, I have seen both the benign and malignant phases in all kinds of hypertension except that due to coarctation of the aorta in which I have never seen the malignant phase.

THE REVERSIBILITY OF THE MALIGNANT PHASE

By far the most important prediction of the hypothesis was, however, that it should be possible to reverse the malignant to the benign phase by lowering the arterial pressure, provided that the renal or other factors had not become so altered as to be incompatible with life. This was actually suggested this by Hollenhorst and Wagener (1949), recorded occasional cases in which sympathectomy abolished hypertensive neuro-retinopathy; and evidence was collected suggesting that the same operation prolonged life in the malignant phase (Woods and Peet, 1941, Hammarström and Bechgaard, 1950; and Smithwick, 1951). Reduction of arterial pressure and reversal of hypertensive neuro-retinopathy were also observed by Page and Taylor (1949) in response to pyrogens, by Kempner (1948) in response to a rice fruit diet and by Smirk and Alstad (1951) to hexamethonium bromide.

More conclusive evidence was obtained by Wright, Heptinstall and myself (1952) in three cases of pyelonephritis with gross hypertension, hypertensive neuro-retinopathy, and arteriolar necroses in both kidney and adrenal tissue removed at operation (Figs. 13, 2 and 3). Excision of a unilaterally diseased kidney in one, sympathectomy and subtotal adrenalectomy in the second, and subtotal adrenalectomy in the third reduced arterial pressure and abolished the retinopathy. All these patients were well five to six years postoperatively, with mild to moderately severe hypertension, no retinitis and no uræa retention. They remain unaltered at the present time of writing, seven

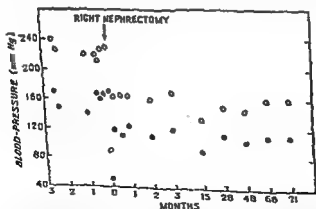


FIG 13.1 Shows the arterial pressure before, and for six years after, excision of a small hydronephrotic pyelonephrotic kidney on 25th February, 1943. The fundus before and after operation is shown in Figs 12.6, 7 and 8. The arteriolar necroses are shown in Figs. 13.2 and 3 (Pickering, Wright and Heptinstall (1952), *Lancet*, ii, 952)



FIG. 13.2

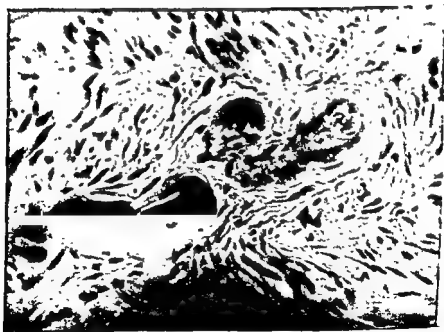


FIG. 13.3.

FIGS 13.2 and 13.3. Arteriolar necroses in adrenal and kidney removed in patient whose fundus is shown in Figs. 12.6, 7 and 8 and whose arterial pressure in Fig. 13.1. Original Microphotographs, Pickering, Wright and Heptinstall (1952), *Lancet*, ii., 952), Figs 5 and 6

unchanged (Fig. 12.5). Seventeen months after operation the fundus had returned to normal (Fig. 12.6). I last saw him on September 27th, 1954, eight and a half years after operation, when he felt and looked perfectly well. His arterial pressure was 145/115, his fundus normal, his urine free from protein and his blood urea 50 mg. per 100 ml.

Since the introduction of hypotensive drugs which can effectively maintain the arterial pressure at a reduced level . . .

described by Perera (1954) (see p. 239), in which retinopathy and renal deterioration occurred after the arterial pressure had fallen. It seems extremely probable that, in such exceptional cases, we are concerned with a different sequence of events. There is no suggestion of disseminated lupus erythematosus in Perera's case, but that is a disease in which retinopathy, renal deterioration and fibrinoid arteriolar necroses occur, it is not due to hypertension, and, in fact, can be produced by large doses of hydralazine, a hypotensive drug.

Fig. 13.4 provides a rather over-simplified diagram of the concept outlined here.

Age and Sex Incidence

Since Volhard and Fahr (1914), it has been recognized that the malignant phase of hypertension tends to be relatively more frequent than the benign in young, than in old, subjects. This, no doubt, results in part from the increased frequency of secondary hypertension, which is often severe, in young subjects. It may also be as Bechgaard (1954) suggests, that those cases of essential hypertension destined to go into the malignant phase are from the beginning more rapidly progressive, and that this tends to occur mainly in young subjects. The peak incidence of the malignant phase is usually about forty years. In most series males predominate over females (Table 13.1), the average being more than two males to every female. This is very surprising in view of the frequency of chronic pyelonephritis in most series and

TABLE 13.1. *Sex Incidence of Malignant Hypertension.*

Author	Men	Women	Total
Volhard (1918)	30	6	36
Ehrstrom (1918)	21	8	32
Page (1939b)	19	11	30
Bechgaard (1946)	18	6	24
Schottstaedt and Sokolow (1953)	63	41	104
Total	151	72	226

to eight years postoperatively. Clearly here the malignant phase has been reversed to the benign phase by measures that have one feature in common; they reduce blood pressure. More recent experience with hexamethonium compounds now leaves little doubt that the malignant phase can be reversed to the benign by prolonged lowering of arterial pressure (see Chapter 15).

Illustrative Case. The material from one of these patients is illustrated in some detail (Case 1, Pickering, Wright and others, 1946). A male, aged 32, complained of loss of vision and of hypertensive neuro-retinopathy (Fig. 12.4). etc, though his blood urea was 37 mg. per 100 test was up to 2.6 per cent. The right kidney renal and right splanchnic nerves and first and second lumbar ganglia, were excised on February 25th, 1946, the kidney being small with an enlarged pelvis and showed pyelonephritis on histological examination. Numerous arteriolar necroses were found in the excised adrenal (Fig. 13.2) and kidney (Fig. 13.3). The behaviour of his arterial pressure is shown in Fig. 13.1. Two months after the operation the papilloedema and exudates had gone from the fundus, but the star figure remained

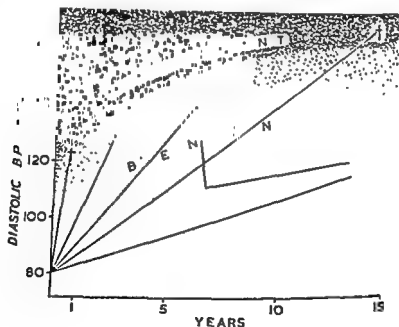


FIG. 13.4. A diagrammatic representation of the relationship between the benign and malignant phases of hypertension.

(shaded zone). The level at which arteriolar necroses develop rises with the duration of the elevated blood pressure.

Finally, the course may be entirely benign, which is indeed usual in essential hypertension.

years of age. Sixty-three persons are now aged 76 or over. The blood pressures of these elderly survivors when they were first examined were : Men, 12 under 200 mm. Hg systolic, none above ; 10 under 110 mm. Hg diastolic, two above ; women, 33 under 200 mm. Hg systolic, 18 above ; 20 under 110 mm. Hg diastolic, 31 above. Thus, in men only the mildest elevation of pressure is compatible with survival to old age, but women withstand a considerably higher range of pressures. Many of these patients were rather obese when they first presented, and the breathlessness on exertion, of which more than half complained, was due more probably to obesity than to a cardiac lesion.

The Influence of Sex

As Table 14 3 shows, most workers are agreed that women have a conspicuously better prognosis than men. Several factors contribute

TABLE 14 3. *Comparison of Mortality between Men and Women with Essential Hypertension.*

Author	Percentage Mortality Females	Percentage Mortality Males
Janeway (1913)	69	86
Blackford Brown and P.	39	70
•	88	93
•	43	71
•	22	41
•	51	60
•	52	72
•	37	69

to this effect. The malignant phase seems to be commoner in men (p 297). Coronary artery disease is much more frequent in men than women. It is also to be remembered that in the population at large arterial pressures tend to be higher in women than in men after middle age (Fig. 8.1).

The Influence of Arterial Pressure

The data from insurance companies presented in Tables 8.8 and 8.9, show clearly that, at any age, expectation of life is inversely related to arterial pressure, the relationship being non-linear over the range studied. Unfortunately, the records of insurance companies, which have the great merit of being collected and analysed by men trained in statistics, stop short at the levels which have hitherto been regarded as normal. Beyond that range we leave insurance statistics

Barker, 1939). These differences cannot be attributed to the therapy employed, as it is doubtful if any effective therapy was available over the relevant period. The world-wide prestige of the Mayo Clinic suggests quite clearly that the very high mortality in their series resulted from the preponderant reference to them of very sick patients. Unfortunately, by no means all the factors determining prognosis can be accurately defined, and comparisons of series, apparently similar, from two institutions, reveal considerable differences between them.

Perhaps the most representative series is that of Bechgaard (1946) who followed for four to eleven years the fate of 1,038 patients who had attended the polyclinic of the Rigshospital, Copenhagen, and who had been found to have an arterial pressure exceeding 160 systolic and 100 diastolic or a systolic pressure over 180. The patients were mostly of the working-classes of Copenhagen, and 81 per cent. were aged between 40 and 69 years. Bechgaard, in collaboration with H. Kopp and J. Nielsen, has now examined the survivors after a further ten years. Excluding (a) patients with definite or questionable nephritis, (b) patients who at the second examination showed normal blood pressure and (c) patients who at the first examination had a fatal disease, such as cancer, he has calculated the mortalities on 828 patients with essential hypertension followed for sixteen to twenty-two years. I am very grateful to him for allowing me to quote extensively from this unique material before it is published.

Their results for the whole series are summarized in Table 14.2. Only two of those patients had been treated with sympathectomy and two with hexamethonium, so that they may be regarded as essentially an untreated series. A fifth of the men and nearly half the women survive after an observation period averaging nineteen years. More than a third of the surviving women are over 70, twenty-one over 80

TABLE 14.2. *Fate of 1,038 Patients with Hypertension who attended the Outpatient Department of the Rigshospital, Copenhagen (Bechgaard, Kopp and Nielsen, unpublished).*

Patients	Number of Patients		
	Men	Women	Total
Original series	325	713	1,038
Dead after 4-11 years	133	160	293
Dead after 16-22 years	229	367	596
Living after 16-22 years	60	297	357
Unidentified			31
Normal blood pressure at first follow-up			54

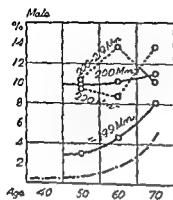


FIG. 14.3.

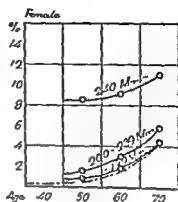


FIG. 14.4.

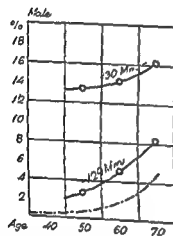


FIG. 14.5.

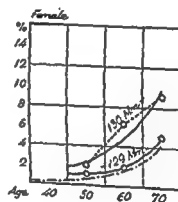


FIG. 14.6.

FIGS 14.3, 14.4, 14.5 and 14.6. Mortality rates for different diastolic pressures: 1" Male diastolic; 14.6, "

women, the mortality is only slightly increased by levels of up to 199 systolic and 129 diastolic. Above that the rates increase, particularly with pressures over 240 systolic, but never to the same rate as in men.

Tables 14.4 and 14.5, from the sixteen to twenty-two year follow-up of Bechgaard's series, relate mortality to age and systolic and diastolic blood pressure at the first examination. The influence of arterial pressure is clearly displayed. At any age and for any blood pressure, the mortality is greater in men than in women. The difference in mortality between those with hypertension and the rest of the population decreases with age. This is a natural consequence of defining hypertension as any pressure above a fixed limit, since, as was

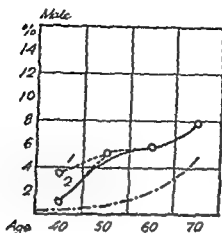


FIG. 14.1.

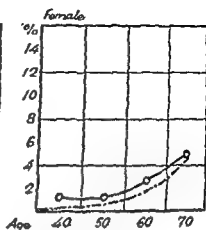


FIG. 14.2.

FIGS. 14.1 and 14.2. Rates of mortality in 1,038 patients with hypertension (continuous line) compared to the rates of mortality in the population (dot and dash line). 1 including glomerulo-nephritis, 2 without glomerulo-nephritis (Bechgaard (1946)).

and enter the confusing world of collections of medical cases. Figs. 14.1 and 14.2 show the rates of mortality for the males and females of Bechgaard's (1946) entire series, as compared with the corresponding rates for the whole population at the same age in Denmark, and Figs. 14.3 to 14.6 show the effects of different levels of arterial pressure.

These figures show that the level of arterial pressure has a very important effect on prognosis, and that this effect differs in the two sexes. In men, the mortalities at the lower levels of both systolic and diastolic pressure shown are about twice the normal rate, and these rates are greatly increased by further rise of arterial pressure. In

TABLE 14.4. Mortality* in a 16 to 22 year Follow-up in relation to Age and Systolic Blood Pressure at First Examination (Bechgaard, Kopp and Nielsen, unpublished).

Age	Men		Women	
	mm. Hg < 199 (per cent.)	mm. Hg > 200 (per cent.)	mm. Hg < 199 (per cent.)	mm. Hg > 200 (per cent.)
49 . . .	486	—	145	440
50-59 . . .	256	700	114	248
60- . . .	141	217	86	133
Total . . .	211	362	105	183

* In this and subsequent figures from the same authors (14.5, 14.6, 14.7, 14.10) the numbers represent the number of dead within the age group by the Danish

blood pressure who is thin. Such was the experience of Hunter and Rogers (1923). But in a larger series followed longer (Bechgaard 1946), this expectation was not fulfilled. Table 14.6 shows the mortality in Bechgaard's final follow-up for men and women whose weights were more than 20 kg. above normal and those whose weights were less. The mortality is about equal in the two series. Frant and Groen (1950) made similar observations. Perhaps these results are due to the erroneously high readings of arterial pressure produced by fat arms.

Effect of Cardiac Symptoms and Signs

Table 14.7 shows the relationship of mortality to myocardial degeneration in Bechgaard's final series. He accepted as indicating myocardial disease: signs of cardiac failure, aortic regurgitation, angina

TABLE 14.7. Mortality in a 16 to 22 year Follow-up in relation to Myocardial Degeneration at First Examination (Bechgaard, Kopp and Nielsen, unpublished).

Age	Men		Women	
	Present (per cent.)	Absent (per cent.)	Present (per cent.)	Absent (per cent.)
-49 . . .	(1,800)	462	350	181
50-59 . . .	1,800	245	475	136
60- . . .	288	135	171	96
Total	544	203	239	121

pectoris, myocardial infarction, perpetual arrhythmia and electrocardiographic changes, applying the usual criteria. The adverse effect is definite at all ages and is much more striking in men than women.

Grant (1933) found that, in general, prognosis in heart disease was adversely affected by signs of cardiac failure and, to a much less extent, by auricular fibrillation, and was inversely proportional to the degree of cardiac enlargement and the reduction in exercise tolerance. Hypertensive heart disease is no exception to the general rule. The influence of cardiac enlargement on prognosis was shown in Table 12.6. Myocardial infarction and angina pectoris are other adverse factors affecting prognosis, particularly in males. Of Cassidy's (1946) 1,000 patients, coronary disease persisted more than twenty years in 11, more than thirty in two. Certain other features of heart disease in hypertension require special attention.

Left Ventricular Failure. Nocturnal dyspnoea, pulsus alternans, and gallop rhythm form a triad which carry a very grave prognosis.

shown, arterial pressure rises with age in the population at large and the means surpass this limit in the older groups, especially in women. And so we find that patients aged 60 and over with "hypertension" below 200 systolic and 120 diastolic have mortalities of 86 and 92 per

TABLE 14.5. *Mortality in a 16 to 22 year Follow-up in relation to Age and Diastolic Blood Pressure at First Examination (Bechgaard, Kopp and Nielsen, unpublished).*

Age	Men		Women	
	mm. Hg < 110 (per cent.)	mm. Hg > 120 (per cent.)	mm. Hg < 110 (per cent.)	mm. Hg > 120 (per cent.)
-49 . .	500	750	170	286
50-59 . .	320	317	120	250
60- . .	144	200	92	139
Total .	221	295	111	189

cent. The importance of considering age in assessing the severity of hypertension is emphasized once more. It would have been interesting to have these figures reassessed in terms of age-adjusted score (Chapter 8).

No other series presents such a detailed analysis of the effect of arterial pressure on prognosis. Burgess (1948), following up 250 cases found the height of the pressure first recorded did not affect prognosis.

Effect of Obesity

Since raised arterial pressure and obesity each affect expectation of life adversely, it would be expected that prognosis would be worse in a patient with hypertension who is fat than in a patient with a similar

TABLE 14.6. *Mortality in a 16 to 22 year Follow-up in relation to Age and Weight at First Examination (Bechgaard, Kopp and Nielsen, unpublished).*

Age	Men		Women	
	< + 20 kg. (per cent.)	> + 20 kg. (per cent.)	< + 20 kg. (per cent.)	> + 20 kg. (per cent.)
-49 . .	620	467	218	155
50-59 . .	347	214	149	161
60- . .	185	173	108	103
Total .	242	229	133	135

The electrocardiographic signs of cardiac ischaemia, particularly T-wave inversion, ST elevation and the appearance of Q-waves, are much too complex to treat here, but will be found in any good contemporary book on electrocardiography. Their prognostic significance is very much that of myocardial infarction and angina pectoris.

Relation to Retinal Changes

In an attempt to obtain better data on which to judge prognosis, Keith, Wagener and Barker (1939) divided subjects with hypertension into four groups, largely on the basis of the changes found in the

TABLE 14.8. *Death at Yearly Intervals after First Examination (Keith, Wagener and Barker, 1939).*

Years	Group 1 (per cent.)	Group 2 (per cent.)	Group 3 (per cent.)	Group 4 (per cent.)
1	10	12	33	70
2	20	23	67	88
3	30	38	78	94
4	30	42	78	98
5	30	46	80	99

eyegrounds. Their classification has been much used and has been described in detail in the last chapter. In Group 1 the retinal vessels showed only mild narrowing or sclerosis. In Group 2 the retinal arteries showed moderate to marked sclerosis. In Group 3 was found retinopathy without papilloedema. "If measurable edema of the disks is added to this picture, the case belongs to Group 4." The yearly mortality for five years is shown in Table 14.8. Smith, Odel and Kernohan (1950) have analysed 2,650 cases of hypertension, having a necropsy at the Mayo Clinic. Three hundred and seventy-

TABLE 14.9 *Cause of Death at Necropsy in Cases arranged according to Keith, Wagener and Barker Classification (data from Smith, Odel and Kernohan, 1950).*

	Total Number of Cases	Cause of Death				
		Cardiac Failure	Coronary Disease	Stroke	Uremia	Unrelated
Group 1.	100	21	7	9	■	60
Group 2.	100	26	20	17	2	35
Group 3.	76	30	9	14	12	11
Group 4.	100	21	1	16	59	3

Such patients may die in their next attack of cardiac asthma and seldom live longer than three years. Each of these manifestations, existing alone, requires more careful scrutiny. Breathlessness at night may be true bronchial and not cardiac asthma, and to distinguish them every effort should be made to witness an attack. In cardiac asthma the patient is usually pale, the breathing rapid, the blood pressure higher than before, and nearly always alternating; the chief auscultatory sounds are medium and coarse râles over the lungs. In bronchial asthma the patient is usually not pale, the breathing is less rapid and the difficulty predominantly expiratory; rhonchi, ranging from squeaks to bubbles, are heard on auscultation. The gallop rhythm carrying a grave prognosis is termed presystolic, because the added sound comes just before the first; it is best heard between apex beat and sternum, and is nearly always associated with tachycardia. This form is to be distinguished from protodiastolic gallop in which the third sound is often the normal third sound occurring soon after the second; heart rate is normal and symptoms absent. Pulsus alternans should always be diligently sought for in a patient with hypertension when the arterial pressure is measured. When the sounds first appear, as cuff pressure falls, they occur at half the rate, to assume the full rate though alternating in intensity at a lower pressure; the difference between these pressures gives the range of alternation and is of prognostic importance. By definition, pulsus alternans assumes a regular pulse. Should there be any reason for suspecting pulsus alternans, such as breathless attacks at night, the patient may be asked to exercise to an extent which is consistent with his habit, and the blood pressure measured again. I have often found, particularly in patients with angina pectoris and myocardial infarction, that pulsus alternans may be observed for a few minutes after exercise even though absent at rest.

Electrocardiographic Changes. Evans and others (1945) found normal electrocardiograms in 41 out of 100 patients subjected to sympathectomy for hypertension. As a rule patients with symptoms referable to hypertensive disease have electrocardiographic changes, chiefly interpretable as due to hypertrophy of the left ventricle (see Sokolow and Lyon, 1949) and to myocardial ischaemia. The changes due to left ventricular hypertrophy include left axis deviation, high voltage and prolongation of QRS, inversion of the T-wave in first and second leads and a depressed RST segment in the first and perhaps the second leads, and in leads over the left side of the heart. These findings are often accompanied by a reciprocally elevated RST segment and upright T in the third lead, and over the right side of the heart. The significance of such changes does not differ from that of other signs of cardiac enlargement.

lesion, 11 were alive three years and five months after the onset of symptoms; nine of 12 males had died, two of a cerebral lesion, three were alive two years and ten months after the onset of symptoms; evidence of a gross cerebral lesion was present in 11, absent in 10, the sexes being combined. It is evident here again that the severity of the retinal vascular lesion is related to life expectation, and that for a given severity of lesion, males fare worse than females.

The Effect of Renal Abnormalities

In view of the bad prognosis of the malignant phase and the frequency of renal involvement in it, renal involvement would be expected materially to lessen the expectation of life in essential hypertension. Proteinuria is of limited consequence. In Bechgaard's series (Table 14.10) the mortality of those with proteinuria was about twice those without. Haematuria without a demonstrable local cause

TABLE 14.10 *Mortality in a 16 to 22 year Follow-up in Essential Hypertension in Relation to Proteinuria at First Examination (Bechgaard, Kopp and Nielsen, unpublished).*

Age	Men		Women	
	Present (per cent.)	Absent (per cent.)	Present (per cent.)	Absent (per cent.)
40	—	375	—	158
50-59	700	270	133	152
60-	200	145	167	95
Total	467	206	200	121

should always suggest the onset of the malignant phase particularly in those whose pressures are very high. A rapidly developing impairment of renal function has a similar implication. When, in the absence of an extrarenal cause, such as vomiting, the blood urea is raised to levels over 60 mg per 100 ml, then prognosis is indeed grave, and such cases respond imperfectly to the hypotensive drugs discussed in the next chapter.

The Effect of Cerebral Lesions

Death is particularly likely to occur during a severe stroke. Death is particularly likely to occur during a severe stroke.

six cases were found in which there was no known cause for the hypertension and enough information to relate the cause of death to the type of retinal change found in life. Their results, arranged under the Keith, Wagener, Barker classification, are shown in Table 14.9. The percentage of deaths from causes unrelated to hypertension falls from 40 in Group 1 to only three in Group 4. The incidence of cardiac failure is fairly steady throughout; that of stroke is much the same in Groups 2, 3 and 4. The chief difference is in the incidence of uræmia, which rises from 3 per cent. in Group 1 to 50 per cent. in Group 4.

As stated in Chapter 12, it seems to me more satisfactory to differentiate the two types of retinopathy characteristic, respectively, of the benign and malignant phases, namely arteriosclerotic retinopathy and hypertensive neuro-retinopathy, on the whole retinal picture and its evolution. That these types of retinal lesion carry quite different prognoses was first clearly shown by Foster Moore (1917). In my own small series (1934), there were 17 patients with hypertensive neuro-retinopathy; all died, five within one month, three in two months, six in six months, one in twelve months and two in nineteen months. Of eight patients with arteriosclerotic retinopathy, one died in twenty months, and the remaining seven were unchanged five to thirty-five months later. The fundus oculi is in fact an extremely important guide to prognosis, not only in being often the first and always the best guide to the onset of the malignant phase, but also in indicating the extent of the lesions of the small vessels.

The relation between retinal and cerebral vascular disease was studied by Foster Moore (1917), who examined the fundi of 44 patients admitted to St. Bartholomew's Hospital for hemiplegia of sudden onset, diagnosed by the physician in charge as due to cerebral hæmorrhage or thrombosis. The blood pressure was available in 30 and was above 200 mm. Hg systolic in 15. The retinal arteries showed no evidence of disease in 30 per cent.; mild or moderate arteriosclerosis in 27 per cent. and severe disease including arteriosclerotic retinopathy in 43 per cent. He also followed up 35 patients with retinal arteriosclerosis, and 31 with arteriosclerotic retinopathy, who had attended Moorfields Eye Hospital for failing vision. The average systolic pressures were respectively 211 and 222 mm. Hg. Of those with retinal arteriosclerosis, four of 14 females traced had died of cerebral hæmorrhage, 10 were alive four and a half years after the onset of symptoms; six of 15 males traced had died, one of cerebral hæmorrhage; nine were alive three years after the onset of symptoms; evidence of a gross cerebral vascular lesion was present in 11, absent in 15, the sexes being combined. Of those with arteriosclerotic retinopathy, eight of 19 females traced had died, five of a cerebral

They studied 192 males and 238 females, and found that mortality at four and eight years rose with the grade and was greater in males than females. In Grade 1 mortality rose with age, but not in Grades 2 and 3. Bechgaard and Hammarström (1950) and Hammarström and Bechgaard (1950) used rather similar groups with the significant exception that "Group 4 comprises patients with malignant hypertension evidenced by definite retinal exudates and/or papillary protrusion with or without retinal hemorrhages and a progressive course of the hypertensive disease." Smithwick (1951) has used a more elaborate grouping in which points are awarded, ranging from one point for such features as enlarged heart, and aged 50 or over, to four points

TABLE 14.11. *Comparison of Survival Rate (as percentages) in Grade IV (Malignant Hypertension).*

Years	Keith, Wagener and Barker (1939)	Palmer, Loofbourow and Doering (1948)	Hammarström and Bechgaard (1950)	
			Men	Women
1	21	—	67	72
2	12	—	42	56
3	6	—	22	36
4	2	20	15	16
5	1	—	15	12

for nitrogen retention, and in which the patients are arranged in four groups according to their total score of points.

The purpose of these elaborate systems of grouping is to guide and to assess the effects of treatment. However, they are only relatively useful for this purpose as may be shown by Table 14.11, which compares the rates of survival in the fourth grade (malignant hypertension) in three of the above series. It will be seen that these differences are very striking. In part they may be due to small differences in the criteria of selection. Part of the difference may have been due to observer error. And part may have been due to differences in social class, or other possibly relevant factors, in the various series. Whatever their source, these differences in survival rate carry one very clear warning: if the efficacy of any method of treatment is to be assessed justly, whenever possible the composition of the control sample must be undoubtedly the same as that of the treated series. There is only one method of achieving this, namely by selecting a series of . . . by the same criteria . . . or treated . . .

if a hæmorrhage is the cause. With thrombosis, bronchopneumonia is one of the chief dangers ; using antibiotics, many patients recover consciousness. Recovery of function varies from complete recovery to severe motor and sensory paralysis with gross defects in personality. The prognosis as regards function is inversely proportional to the duration of coma and directly proportional to the speed with which function is recovered after consciousness is regained. With a resolute patient and a good physiotherapist, recovery in function may go on for eighteen months. In general, recovery of function is better the younger the patient.

The fate of patients who have had a cerebral vascular accident is as variable as of those with coronary artery disease. Some survive for long periods, have no further attacks and die of something else. Louis Pasteur lived for eight years after an attack in which he lost his speech and which, it would seem from a cartoon by Spy, left him with a partial paralysis. He died of a more widespread paralysis at the age of 73, but his major scientific work was finished before his stroke. Some have another stroke or a myocardial infarct soon afterwards. Yet others may survive as a sort of decerebrate preparation unable to talk or feed himself, unable to recognize his relatives, unable to get out of bed, and doubly incontinent. Such patients provide some of the great ethical and social problems of this antibiotic age.

More Elaborate Classifications

Recent classifications have attempted to take into account the extent to which organs other than the eye can be recognized as involved in the consequences of hypertension. The next after that of Keith, Wagener and Barker was due to Palmer, Loofbourow and Doering (1948) who again used four groups, which were as follows :

- Group 1. No, or minimal, changes in fundi. Normal heart or slight hypertrophy of left ventricle. No impairment of renal function. Normal urine or slight protein and changes in the sediment.
- Group 2. Fundus : irregularity of arteries and arteriovenous compression. Heart usually enlarged, not functionally impaired. Kidney normal or slight abnormality in function and urine.
- Group 3. Fundi : often hæmorrhages and exudates. Heart often enlarged with functional impairment. Urine, frequently protein and casts, renal function often impaired. Cerebral accidents common.
- Group 4. The obligatory sign is œdema of discs with or without recent exudates.

CHAPTER 15

THE TREATMENT OF HYPERTENSION

THE treatment of patients with hypertension can be considered under the following headings: the discovery and, if possible, removal of the cause of hypertension, the treatment of associated conditions that cannot be removed, the treatment of hypertension itself and the treatment of the complications. As always in the treatment of the sick, it is extremely important to remember that we are dealing with sentient creatures who have a mind as well as a body. It is necessary to consider the patient's reaction not only to his affliction but also to the measures used by his doctor.

REMOVAL OF THE CAUSE OF HYPERTENSION

Future chapters will show that the cause of hypertension can be removed in the following conditions.—

(1) Unilateral renal disease, nearly always pyelonephritis, by excision of the kidney (Chapters 17 and 18).

(2) Coarctation of the aorta by surgical repair (Chapter 22).

(3) Pheochromocytoma, by excision of the tumour or tumours (Chapter 20)

(4) Cushing's syndrome, by removal of an adrenal tumour, or, if no such tumour exists, then by bilateral adrenalectomy (Chapter 21).

(5) Relief of urinary obstruction, e.g., by prostatic adenoma, occasionally materially and persistently reduces arterial pressure.

It is extremely important, therefore, that any patient in whom the arterial pressure is high should be thoroughly investigated to make sure whether any such condition exists (see Chapter 24). However, as will be described, in many of those patients in which such a cause is found and removed, the arterial pressure remains high. The hypertension may then require treatment in the same way as in essential hypertension

TREATMENT OF CONDITIONS THAT CANNOT BE REMOVED

The practical management of nephritis, pyelonephritis, polycystic kidney and polyarteritis nodosa will be considered in the appropriate chapters

In polyarteritis nodosa, cortisone will prevent fresh lesions, and in pyelonephritis it is possible that antibiotics may arrest progress

able ethically, and in this particular example treated groups have to be compared with past series in which no treatment was given.

SUMMARY

Prognosis in essential hypertension depends on the following factors :

- (1) The height of the blood pressure. In conformity with the data described in Chapter 8, blood pressure needs to be considered in relation to age. A given high value for blood pressure more greatly curtails expectation of life in a young than in an old subject.
- (2) Sex. For any given high blood pressure at any age, women seem to fare better than men.

Expectation of life is reduced by the following :

- (1) The onset of the malignant phase, as indicated particularly by hypertensive neuro-retinopathy, by progressive renal failure and less certainly by unexplained hæmaturia and a very high pressure.
- (2) Cardiac asthma, pulsus alternans and gallop rhythm, or less certainly by any one of the three.
- (3) Congestive cardiac failure.
- (4) A cerebral vascular accident.
- (5) Myocardial infarction or angina pectoris.
- (6) Other rarer forms of vascular accident, e.g. dissecting aneurysm of the aorta.
- (7) Retinal arteriosclerosis.

Moderate hypertension, particularly in fat, elderly women, seems to carry so good a prognosis that no treatment for hypertension seems justified.

has, in fact, increased the expectation of life of patients with hypertension; but it is certain that this treatment has made it much more difficult for the patient to experience any "joie de vivre." In this context may be quoted the remarks of Weiss (1939) on past treatment: "What has been done in an effort to reduce the blood pressure? Because of an ill-founded idea that protein was responsible for hypertension and kidney disease the patient was denied meat and eggs, and especially red meat, which for some reason was looked upon with particular dread. His diet was rendered even more unpalatable by the withdrawal of salt. Sympathy would doubtless have been extended to this half-starved fellow except that he probably was not able to eat anyway, his teeth having been extracted on the theory that focal infection had something to do with hypertension. Even before this he had sacrificed his tonsils and had had his sinuses punctured because of the same theory. In case some food has been consumed, the slight colonic residue was promptly washed out by numerous colonic irrigations, especially during the period when the theory of auto-intoxication was enjoying a wave of popularity. To add to his unhappiness he was often told to stop work and exercise. Of course, he was denied alcohol and tobacco as well as coffee and tea, and as a climax to the difficulties of this unfortunate person, he may now fall into the clutches of the neurosurgeon, who is prepared to separate him from his sympathetic nervous system."

Common Sense and Symptomatic Treatment

As was pointed out, the evidence of hypertension is often not experienced until after the patient learned he had high blood pressure. Owing to the well-known importance of maladies associated with hypertension as causes of death, and to articles in the popular press, the public has a profound fear of high blood pressure, a fear which often leads to a diagnosis of hypertension if some exacting and arbitrary standard is instituted. In no condition is it more important that the doctor should avoid this fear of the patient, or if it is necessary to instill it, that it should be based on a realistic basis.

It is also true that about one-third of all patients with essential hypertension die of an immediate cause. As in any other condition, the doctor has a great responsibility.

pressure usually persist, and the hypertension may require treatment in precisely the same way as essential hypertension, where the cause can as yet be neither identified nor removed.

TREATMENT OF THE HYPERTENSION ITSELF

General Considerations

Successful treatment demands a clear appreciation of what it should, and can, achieve. The twin objectives are the prolongation of life and the encouragement of the sense of well-being or enjoyment that the patient derives from his life while he has it. These two objectives are often in conflict, and in no condition more than that here considered, where all apparently successful forms of therapy have a high nuisance value.

In trying to achieve a satisfactory compromise between these two objectives, the decision of the doctor should be based on a precise knowledge of the effects of the treatment, on the expectation of life, and incidence of complications. Unfortunately, in no single instance of the measures here to be considered is that information to hand. The extension of the scientific method to therapeutics has equipped us with a new tool of some modest precision, namely, the clinical therapeutic trial. Here, a group of subjects is chosen on an agreed basis, and allocated at random to two or more groups, one of which receives the specific therapy and one of which serves as a control. Ideally, the control series should receive a dummy treatment and neither the patient nor the doctor should be aware what each patient receives until the trial is completed (see Hill, 1951).

The best that has been done with the remedies at present available is to compare the results in a treated series with an untreated series published by other workers or with an untreated series selected in retrospect to compare with the treated. These methods contain fallacies which will be considered later.

In the past, treatment has been based upon that negation of the scientific method called "Applied Pharmacology." First an unproven hypothesis as to the nature of the disease is accepted. From the action of a particular drug or other measure on an animal of another genus, often under an anæsthetic, and using the drug in quite different doses, an appropriate form of therapy is worked out and applied. There could be no quarrel with this as a first step in the institution of a clinical trial. But, unfortunately, in the past, this final and decisive step has been omitted and should the therapy be sufficiently plausible or be backed by sufficient authority, it starts what might justifiably be termed a wave of mass hysteria. Looked at from the vantage point of years later, it is at least extremely doubtful whether past treatment

(3) Otherwise unexplained hæmaturia and proteinuria in the presence of a grossly raised arterial pressure.

Once we leave the malignant phase, the indications become less certain; but the following indications seem clear cut:

(4) Cardiac failure; or undue breathlessness on exertion associated with cardiac enlargement in a patient with a high diastolic pressure.

(5) Hypertensive fits.

(6) A diastolic arterial pressure persistently of 140 or over in a patient aged 40 or more, or diastolic persistently of 130 or over in a patient aged less than 40. The discovery of an effective treatment with a low nuisance value will reduce these limits.

Much more controversial are:

(a) Cerebral vascular accidents.

(b) Angina pectoris and myocardial infarction, because of the occurrence of cerebral and cardiac infarction during periods of low arterial pressure produced by any of the remedies. I would suspect that it will eventually be shown that more is to be gained than to be lost by controlling arterial pressure in cerebral and cardiac vascular occlusion. But it is possible that a low fat diet or anti-coagulant treatment may be even more important. These questions cannot, however, be answered without the proper therapeutic trials. Smirk, Doyle and McQueen (1934) reviewing four and a half years' experience with methonium therapy, note that the occurrence of cardiac asthma and congestive failure have been greatly reduced, but that some of their patients apparently saved from these disasters died from strokes. "Prevention of strokes is the major problem remaining."

On general principles, and particularly in view of the new concept of high blood pressure as a graded characteristic, it would seem probable that the efficacy of reducing arterial pressure, in prolonging life and abolishing symptoms, will depend on the height of the arterial pressure. Thus a much greater effect on cardiac failure may be expected of such therapy in a patient with pressure of, say, 250/160 than in one with a pressure of 180/120. It is again misleading:

SYMPATHETOMY

Extensive excision of the paravertebral sympathetic ganglia had its origin in the hypothesis that high pressure is due to over-action of the sympathetic nerves. The operation has been very extensively practised, but its usefulness is still far from plain, largely owing to the fact that it has never received a properly organized and controlled clinical trial.

Immediate
deter

deal with any new development that may arise. This applies to all, and in milder cases and older subjects it may be all that is required.

Obesity

Since it is well known from insurance companies' statistics that expectation of life is decreased by obesity, it is reasonable to suppose that obesity also prejudices the patient with hypertension, despite the fact that in Bechgaard's (1946) series this expectation was not fulfilled. By general consent, obesity, if present, should be treated by dietary means in the ordinary way. As was seen on page 208, this may produce a considerable fall in arterial pressure. It is, however, right to emphasize that it is quite uncertain whether reduction in weight improves prognosis.

MEASURES TO REDUCE ARTERIAL PRESSURE, THEIR USEFULNESS AND LIMITATIONS

A large number of remedies have been introduced, had their vogue for a while and been discarded. Amongst these are the nitrites, thiocyanates, the dehydrogenated alkaloids of ergot and the injection of pyrogens. Those surviving into current practice are: sympathectomy, adrenalectomy, salt-poor diet, *veratrum viride* and its extracts, the methonium compounds *hydrallazine* and *Rauwolfia* extracts. So far as can be judged at present, methonium compounds offer by far the most promising form of therapy, especially in combination with *hydrallazine* or *Rauwolfia*.

INDICATIONS FOR LOWERING ARTERIAL PRESSURE

In the absence of controlled clinical trials we have to discuss these indications on the basis of our, as yet, imperfect knowledge of the rôle of arterial pressure in the production of lesions. Its most direct and important rôle is probably in the production of arteriolar necroses which, as we have seen, are probably the consequence of the level of arterial pressure, and the rapidity with which that level was reached. We can accept three as absolute indications:

(1) The onset of the malignant phase, as judged by the presence of bilateral papilloedema or large ill-defined exudates in association with a grossly raised or a recently raised arterial pressure

The rôle of hypertension in the production of left ventricular failure is also clear enough to make another absolute indication:

(2) Left ventricular failure in the presence of a grossly elevated arterial pressure.

Since arteriolar necrosis may begin in the kidneys before hypertensive neuro-retinopathy, another indication is:

very careful analyses of patients treated medically and by sympathectomy, which show that sympathectomy has greatly improved the expectation of life. Hammarström and Bechgaard collected 251 cases operated on at the Serafimer Hospital, Stockholm, and followed up for two to eight years, and 435 non-operated controls selected retrospectively by the same criteria as the operated cases from 130,000 records of various Copenhagen hospitals and St. Erik's Hospital, Stockholm. They divided these cases as follows: Group 1 symptomless, Group 2 with symptoms but without cardiac enlargement; Group 3 with cardiac enlargement, cerebral insults or constant albuminuria, Group 4 with retinal exudates and/or papillary protrusion. There were no operated cases in Group 1, and in Group 2 the mortality in the non-operated cases was low enough to require longer observation to establish a significant difference. But in Groups 3 and 4 the prognosis was considerably better in the operated group, the difference being statistically significant in Group 4. Unfortunately, it is extremely hard to be sure that series selected in retrospect are in fact truly comparable. There was, for example, a considerable age difference between the two series, the average being 43 years in the operated, and 49.6 years in the unoperated group. Smithwick has compared the mortality rates in his very extensive series of sympathectomized patients with those of Keith, Wagener and Barker (1939) and of Palmer, Loofbourow and Doering (1948) employing their classifications, the results being strikingly in favour of the operated cases. Impressed by the fallacies in selection, he has also compared the mortality rates in his operated cases with those cases referred to him but not operated upon, using a system of grouping along the same lines but more comprehensive. This also shows a very striking difference in favour of sympathectomy. Even here, however, a possible source of error does not seem finally to have been ruled out. What factors determined why some patients were subjected to surgery and can these factors have determined the differences in survival between the two groups?

To sum up, it would seem probable that sympathectomy is strikingly perhaps, mortality such as severe pain of a causalgic type, and giddiness and palpitations on standing and on effort. The major difficulty, which has not yet been solved, is to determine in advance which patients will react well and which badly.

BILATERAL ADRENALECTOMY

Many of the earlier surgical enthusiasts who treated hypertension used to remove the medulla and parts of the cortex of the adrenals

few, the pressure quickly regains its previous level; in a few it remains low persistently; in most it slowly rises to about its pre-operative value. Thus, in the combined series published in Great Britain by Chris (1951) (33 cases), Platt and Stanbury (1950) (80 cases) and Northfield (1948) (29 cases), significant reduction in pressure was achieved in 26 out of 142 or 18 per cent., at about two years after operation. In the series studied by Evelyn and his colleagues (1949), 21 per cent. of the patients operated on had a significant reduction of pressure at the end of five years. Surgeons have tended to attribute these recurrences of hypertension to over-activity of the remaining sympathetic nerves and, striving always for perfection, have successively extended the operation. Thus the early operations of Peet on the splanchnic nerves and thoracic ganglia above the diaphragm, and of Adson on the splanchnic nerves and lumbar ganglia below the diaphragm, were combined by Smithwick, while Grimson ablates the whole sympathetic chain from T2 to L3 on both sides. It is not clear, however, that the results in terms of comfort or longevity are much better with the larger than the smaller operations, while the persistence of hypertension in many cases after a nearly complete sympathectomy (Grimson, 1942) makes it unlikely that, in these cases at least, hypertension was due to overaction of the sympathetic nerves.

There have undoubtedly been a small proportion of outstanding successes from the operation. In a few cases in the malignant phase of hypertension, whether this complicates essential hypertension, pyelonephritis, or chronic nephritis, there is a good fall of pressure, the eyegrounds clear, urinary abnormalities regress and life is prolonged. The same occurs in some cases in the benign phase; there is nearly always relief of headache, frequently of giddiness and less certainly of cardiac failure. But in most patients in the malignant and many in the benign phase, the disease pursues its relentless course. And the chief difficulty, now universally admitted, despite early enthusiasm, is that there is no certain way of distinguishing between those in whom the operation will succeed and those in whom it will fail, even by employing batteries of sedation, cold pressor, tetraethylammonium and other tests. In general, it would seem that the younger the patient and the more recent the hypertension, the greater is the probability of success, and again, provided renal function is good, irrespective of the underlying lesion. The effects of a therapy are rightly judged, not on isolated blood pressure readings, but on the well-being of the patient and on his expectation of life. Woods and Peet (1941) showed that their patients with malignant hypertension, treated by sympathectomy, survived for a significantly longer time than the unoperated series of Keith, Wagener and Barker (1939). Hammarström and Bechgaard (1950) and Smithwick (1951) have published

was a contraindication to it, and that its usefulness was worth exploring further.

Their observations on the effects of total adrenalectomy on arterial pressure are of great interest from the point of view of the hypothesis that a disturbance in the secretion of these glands plays an important rôle in the pathogenesis of the disease. It is to be noted that only in a minority of patients was the arterial pressure restored to normal. Of these they write, "In those patients whose blood pressure has fallen in response to adrenalectomy it has been possible to restore the blood pressure toward the original hypertensive levels with DCA, occasionally even with small doses such as 2.5 mg daily, or large supplements of sodium chloride (6 to 9 gm. daily) administered for only a few days."

Jeffers and others (1953) and Lukens (1953) described the results in 82 patients with severe hypertension, aged less than 55, with a diastolic blood pressure over 120 mm. Hg, a blood urea nitrogen under 20 mg. per 100 ml, and a phenolsulphonephthalein excretion of over 15 per cent in 15 mins. Of these 11 had a subtotal adrenalectomy, 56 a subtotal adrenalectomy and sympathectomy, two a total adrenalectomy and 13 a total adrenalectomy combined with sympathectomy. The results are summarized in Table 15.1.

My own view is that subtotal or total adrenalectomy has now little or no place in the treatment of hypertension. Not only is life without adrenals very precarious even with our present array of substitution products, but the results with the methonium salts, with or without hydralazine and Rauwolfia are so promising as to suggest effort should be canalized in this direction.

TABLE 15.1. *The Effects of Subtotal or Total Adrenalectomy combined with Sympathectomy in 82 Patients with Severe Hypertension (Jeffers and others, 1953).*

Smithwick group	Normal blood pressure (140/90 or less)	Elevated B P lying, normal B P standing	No change B.P., symptoms unproved	No change B.P., unimproved	Dead
1	0	0	0	0	0
2	8	5	8	0	0
3	6	4	5	0	2
4	7	4	16	0	17

LOW SALT DIET

A severe restriction of salt intake has been used for many years in French and German clinics in the treatment of oedema, nephritis,

on the two sides, as well as large parts of the abdominal sympathetic nervous system. These operations fell into disrepute. Stimulated by the results obtained by Goldblatt and his colleagues in dogs whose renal arteries had been clamped (see page 110), in 1946 I asked my colleague, Mr. Dickson Wright, to remove the whole of one and three-quarters of the other adrenal in three children with pyelonephritis with hypertension in the malignant phase in whom the disease was bilateral, or in whom nephrectomy had not abolished the retinopathy or materially reduced blood pressure; in one of these an infra-diaphragmatic sympathectomy was simultaneously performed. Only one of these patients developed Addisonian pigmentation; but in all, the operation appeared to reduce blood pressure; all recovered and all remain alive and well at the time of writing, 1954. I, therefore, asked him to perform the operation in three adults with hypertension in the malignant phase; none of these improved, and in none did the course of the disease seem modified, and so I abandoned the operation.

Since the advent of cortisone, total adrenalectomy has seemed less fearful and has now been carried out in a number of clinics. The experience of two may suffice. Thorn and others (1952) report the effects of a complete bilateral total adrenalectomy in fifteen patients with severe hypertensive vascular disease. The idea of the operation arose from observations on a male of 59 with progressive Addison's disease who, in 1939, had an Addisonian crisis in which his arterial pressure fell to 130/90, rising after insertion of ten pellets of DCA to 220/100 and falling, after eight pellets were removed, to 130/70.

Of the fifteen patients whose adrenals were totally removed, nine survived three months or longer. Of these nine, definite improvement in the arterial blood pressure occurred in two patients: a male of 29 with arterial pressure 180/120 to 230/180 and glomerular filtration rate (GFR) 128-136 ml. per min., whose blood pressure postoperatively was 130/90 to 150/100, and who died suddenly eleven months after operation, and a male of 26 with long-standing proteinuria and six months hypertension, bilateral neuro-retinopathy, GFR 82-98, renal biopsy no abnormality, whose blood pressure eighteen months after operation was 160/120 and whose fundi then showed no papilloedema or exudates. Temporary improvement in blood pressure occurred in one patient who died suddenly three months after operation. In three patients there was improvement in symptoms without improvement in blood pressure; three were unimproved and six were dead. All patients who survived showed a great increase in the excretion of sodium and chloride. In the three patients studied, renal function declined. They concluded that the operation was feasible, that nitrogen retention

In using this diet it is essential to check the urinary excretion of sodium or chloride which should not exceed 300 mg. NaCl or 5 m. eq. Na per day, and to estimate the blood urea at frequent intervals to prevent a fatal uræmia.

VERATRUM ALKALOIDS

Veratrum alkaloids were used first in the treatment of eclampsia by Baker in 1859. The pharmacology of these substances is summarized by Kraye and Acheson (1946). The fall of blood pressure is produced by vasodilatation and a vagal effect on the heart, excited reflexly from receptors in the heart and lungs (von Bezold reflex).

Wilkins (1951) and Kauntze and Trousce (1951) have reported the successful lowering of arterial pressure by "Veriloid," a proprietary preparation given by mouth four times a day for periods of up to three years (Wilkins). Wilkins begins with 2.0 mg. four times a day and increases the dosage, according to the effect produced, up to 5.0, 4.0, 4.0 and 5.0 mg., noting that a dose in excess of that amount is usually not more effective in lowering arterial pressure. The fall of arterial pressure begins 45 to 150 minutes after oral administration.

one to seven hours.

blood pressure may l
nausea, vomiting and collapse.

Kauntze and Trousce found that blood pressure was reduced in about two-thirds of their patients, but in half of them the effective dose approached so close to the toxic dose as to make the drug impracticable. Smirk and Chapman (1952) compared treatment by veratrum alkaloids and by hexamethonium bromide. They found that substantial blood pressure reduction without important

Most physicians who use veratrum alkaloids adjust the dose by the patient's blood pressure. Thus, a patient receiving the drug at 8 a.m., 1 p.m., 6 p.m. and 11 p.m. will have his pressure measured just before his dose is due and will adjust the dose accordingly. With such a scheme about one-third of subjects may be regulated very satisfactorily. The main disadvantage is that, even so, attacks of nausea, vomiting and collapse are not infrequent and not wholly predictable. They can be to some extent prevented by phenobarbitone, and they respond to atropine by injection but not to the antihistamine drugs. The social consequences of such a routine are obvious. It seems fair to predict that the veratrum drugs have a definite but limited usefulness in the control of raised arterial pressure.

heart failure, hypertension, angina pectoris, etc. Unfortunately it was usually used uncritically and without careful assessment of its results.

In 1922, Allen and Sherrill reported the treatment of 180 severe cases of hypertension by close restriction of sodium chloride intake for from one month to three years. Pressure was restored to normal in 19 per cent. and treatment failed completely in 55 per cent. of cases. Renewed interest was awakened by the rice-fruit diet introduced by Kempner (1948) who arrived at this diet as the result of experiments on kidney slices, using mental processes that are not accessible to me. The rice diet contains 20 g. protein, 8 g. of fat, 200 mg. Cl and 150 mg. Na and provides 2,000 calories per day. Kempner recommends that the diet may have to be continued indefinitely, but that, provided the clinical state and the arterial pressure allow, additions may be made of non-leguminous vegetables, fish and lean meat, all free from fat and salt. There is general agreement that on this diet the systolic and diastolic pressures of most patients with hypertension fall, and that the pressure remains down if salt-free protein is added, to rise again if sodium chloride is added. Kempner (1948) recorded the results in 500 patients treated by this diet for periods of four to 898 days. The diet was ineffective in 178 patients of whom 26 were in a critical condition and died early. In the patients successfully treated, the average fall of blood pressure was 47 mm. Hg systolic and 21 mm. Hg diastolic. Papilloedema disappeared completely in 17 patients, partially in five and remained unchanged in one patient. In Great Britain a committee of the Medical Research Council (1950) confirmed these findings on 36 patients, in whom the average fall of blood pressure was 55 mm. Hg systolic and 26 mm. Hg diastolic. The rice-fruit diet, or, rather, any diet containing less than 250 mg. salt per day, thus justifies its claim as an effective means of prolonging life in malignant hypertension and in reducing arterial pressure and relieving headache in benign hypertension. It is accepted therapy for prolonged cardiac failure. To what extent it may prolong life in benign hypertension is not established. The therapy has, however, two limitations. The first and lesser, is that it is dangerous in patients with impaired renal function, in whom it may precipitate uræmia. The second and greater is the extent to which it disrupts social relations. It is insipid, unappetizing and monotonous and demands great care in its preparation, for, if the salt rises above 250 mg. per day, the effect in most instances is lost. In Great Britain, it is quite impracticable for a member of a large household with minimum domestic help. In the United States, where salt-free articles are more easily obtained from stores, it becomes a practical proposition. Even then its deadly monotony tends to make it intolerable unless the physician can infuse into the patient some of the asceticism of the religious zealot.

In using this diet it is essential to check the urinary excretion of sodium or chloride which should not exceed 300 mg. NaCl or 5 m. eq. Na per day, and to estimate the blood urea at frequent intervals to prevent a fatal uræmia.

VERATRUM ALKALOIDS

Veratrum alkaloids were used first in the treatment of eclampsia by Baker in 1859. The pharmacology of these substances is summarized by Krayer and Acheson (1946). The fall of blood pressure is produced by vasodilatation and a vagal effect on the heart, excited reflexly from receptors in the heart and lungs (von Bezold reflex).

Wilkins (1951) and Kauntze and Trounce (1951) have reported the successful lowering of arterial pressure by "Veriloid," a proprietary preparation given by mouth four times a day for periods of up to three years (Wilkins). Wilkins begins with 20 mg. four times a day and

... most effective in lowering arterial pressure. The fall of arterial pressure begins 45 to 150 minutes after oral administration and continues

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METHONIUM COMPOUNDS

The original investigations on these substances were by Barlow and Ing (1948) and Paton and Zaimis (1949). Paton and his colleagues have shown (Paton, 1951) that they act on sympathetic and parasympathetic ganglia, probably combining with the receptor substance on the postganglionic nerve endings, thus preventing synaptic transmission. In larger doses, they paralyse other effects transmitted by acetylcholine such as motor nerve stimulation. Arnold and Rosenheim (1949) showed that these substances, injected intramuscularly, had a greater depressor effect in patients with essential hypertension than in normal subjects, and that in both, the assumption of the upright posture produced a profound fall of pressure during the action of the drug. Arnold, Goetz and Rosenheim (1949) and Burt and Graham (1950) observed increased skin blood flow, as is to be expected, but the former found that some increase occurred in the sympathectomized limb. With small doses which produce a small fall in arterial pressure, the cardiac output in the recumbent position may increase, while the total peripheral resistance falls. Larger doses produce a fall in cardiac output in the recumbent position with a decrease (Werkö and others, 1951), no change, or an increase in peripheral resistance (Grob and others, 1953). In the erect position, the cardiac output falls, but no more than in this position before hexamethonium was given (Gilmore and others, 1952); the fall of pressure is attributed to a failure of postural vasoconstriction (Grob and others, 1953), particularly on the vessels of the lungs (Gilmore and others, 1952). Coronary blood flow was unchanged by hexamethonium but renal blood flow was at first decreased, later returning to normal (Grob and others, 1953). The rise in arterial pressure which occurs in exercise may be converted into a fall by doses which reduce only slightly the arterial pressure in the upright posture (Rønnov-Jessen, 1953; Fowler and Guz, 1954).

The clinical results achieved with these drugs have varied very greatly, and there is no doubt that their successful employment requires a considerable understanding of their mode of action and great attention to detail (see reviews by McMichael, 1952; Pickering, 1952a; and Smirk, 1953b). Smirk has been, perhaps, their most consistent and persistent advocate and his account will here be largely followed, because, in general, my own less extensive experience agrees with his.

Of the various methonium compounds used, two have proved the most successful, Hexamethonium bromide (or Chloride or tartrate) and M and B 2050A, Pentapyrrolidinium or Ansolysen. Both these substances produce transient falls of arterial pressure increased by erect posture.

Hexamethonium bromide is relatively ineffective and unpredictable

in the experience of most of my colleagues and myself when administered by mouth. Milne and Oleesky (1951) showed that nearly all the hexamethonium injected intramuscularly is excreted in the urine, but only a fraction, which may vary from 3 to 13 per cent. from one day to another, of that given by mouth. Absorption from the gut is thus irregular, and dangerously large falls of arterial pressure may occur unpredictably in patients receiving large oral doses. Moreover, bromism may occur, particularly in patients receiving a diet low in salt. Subcutaneous injection is more reliable, the arterial pressure showing its maximal fall about one hour, and returning to normal about four hours, after injection. With hexamethonium bromide or chloride, the injections have to be given six or eight hourly, thus four or three times a day, beginning with 25 or 50 mg. subcutaneously, the dose is increased as tolerance rises, until the final dose is 250 or 300 mg. three times a day. In one patient quoted by McMichael (1952) the dose reached 750 mg. subcutaneously given as 2.5 ml. of 30 per cent. solution deeply under the skin, with a little procaine to avoid the pain otherwise produced.

Pentapyrrolidinium bitartrate (pentolinium) can be used by mouth. It is not well absorbed (Harrington, 1954), but is effective in small doses. Its maximum effect is at between one and a half and three hours, and its effect may last six to eight hours. The second dose of the day may produce a relatively larger effect. Smirk (1953a) finds that, when a fully effective oral dose of pentapyrrolidinium is given before breakfast, a very small additional dose is required before lunch to extend the activity into the early evening. A further dose should be given before going to bed and McMichael recommends that this should be about twice the morning dose. In other patients, in my experience, more frequent dosage at eight, twelve, four and ten may be desirable. A suitable initial dose is 20 mg. and this will require increase until tolerance is stable and a suitable effect produced. The dose may vary from 100 to 700 mg. Unfortunately, with pentapyrrolidinium, the absorption, which is delayed by meals, is also irregular. "Where capricious alimentary absorption is combined with a critical dosage level a bewildering variation of response may be encountered" (Smirk, 1953a).

Pentapyrrolidinium by subcutaneous injection produces a fall of arterial pressure maximal at about one hour and lasting about six. It has usually to be given three times a day to get effective control, though in some patients two injections may suffice. In the case of hexamethonium, the dose may be 12.5, 12.5 and 37.5 mg. of the day may be given. It is sometimes found that the evening dose has to be two or three times the earlier doses. Thus, one of my patients, a doctor, injects himself with 12.5, 12.5 and 37.5 mg.

pentapyrrolidinium at 8 a.m., 2 p.m. and 10 p.m. respectively. The highest dose reached by Smirk (1953b) was 70 mg. twice daily (in polyvinyl pyrrolidone solution). Smirk has found that both hexamethonium bromide and pentapyrrolidinium dissolved in 25 per cent. polyvinyl pyrrolidone give more prolonged effects, so that two injections a day may suffice. Rosenheim (1954) finds polyvinyl pyrrolidone does not effect response or excretion.

The most reliable effects with both substances are thus obtained by subcutaneous injection. The management of these patients closely resembles the management of the diabetic with insulin, the substance used, its mode and frequency of administration, and its dose, being adjusted to the individual patient by its effects. Just as in the early days of insulin, therapy was controlled by estimation of blood sugar, so in this, it is controlled by estimation of arterial pressure. These substances are therefore difficult to use effectively in the absence of an organized clinic, with technical help in the estimation of arterial pressure. The aim of treatment is to adjust the lowest blood pressure, with the patient standing, to the neighbourhood of 120 systolic 80 diastolic, to maintain the pressure persistently below 120 diastolic, and to avoid side effects; and this is no easy matter. Treatment may begin in or out of hospital, so long as the blood pressure can be measured frequently and the patient is near expert attention; for the treatment has its dangers. Blood pressures are measured in both the sitting and standing postures or sitting only if the patient is confined to bed. Since the effects are greatest in the erect posture, patients should be up and about where possible. Smirk's patients attend the technicians' rooms daily for seven hours a day for five days a week (New Zealand has a forty-hour week), usually for three weeks, the blood pressure being measured at twenty-minute intervals. Others, like myself, prefer to start the patient as an in-patient, have to be content with hourly, two-hourly or less frequent readings but throughout the day and for the full week. The dose is adjusted in accord with the pressures registered and with the side effects. After the patient is discharged he attends weekly, later monthly, when blood pressures should be recorded for as long periods as are practicable. As Smirk has pointed out, single estimations of casual pressure are often very misleading. The only effective control, in the absence of frequent blood pressure readings, is by hypotensive symptoms, not by side effects such as a dry tongue and blurred vision. The dose is increased by very small increments until mild hypotensive symptoms occur when the patient stands still for sixty seconds at the time when the action of the drug is at its height; then the dose is reduced by correspondingly small increments until the hypotensive symptoms become inconspicuous. We and others find that control is not often effective unless mild hypotensive symp-

oms occur in this test. Hypotensive symptoms in general consist of feelings of faintness, unsteadiness and lightheadedness or there may be a strong sensation of fatigue and a desire to flop down in a chair.

Employed in this way Smirk (1953b) records the following effects on 250 patients treated for periods up to three and a half years :

" With effective treatment involving reduction of the blood pressure to normal during the troughs of the blood pressure falls, papilloedema, retinal exudate both soft and hard, and retinal hæmorrhages disappear in almost all cases. Where papilloedema has impaired vision, vision improves. Three to six months' intensive treatment is sometimes required to produce the improvement mentioned in papilloedema, and as long as twelve months may be needed to disperse a star-shaped macular figure. Hypertensive headaches are substantially, often completely, relieved and hypertensive dizziness usually disappears. With an effective régime there is usually a definite amelioration within a week. Attacks of cardiac asthma will usually cease and congestive heart failure disappears, with improvement in exercise capacity. Of twenty-seven patients under sixty years six did not work, eleven men returned to gainful employment (one died later from stroke) and ten women were engaged in housework (two died later from stroke). Relief from an attack of cardiac asthma is commonly obtained by the slow intravenous injection of 4 mg. of hexamethonium bromide (or chloride) at two-minute intervals until the blood pressure is near to normal. Larger doses are required in patients already on treatment who have acquired a measure of toleration. Substantial relief from breathlessness in heart failure usually comes with the first few injections which reduce the blood pressure to near normal levels. With continued administration of effective doses patients under 60 whose heart failure is due to the hypertension are usually walking comfortably on the flat, and some are managing a flight of stairs, within a few weeks. In a proportion of cases, depending on the selection of patients (about one in four in our series), the blood pressure reduction alone is not sufficient to relieve cardiac asthma and congestive failure. Even so, although in patients who have failed while on *digitals* it is usually necessary to maintain the same dose for some weeks or months, it is often possible, when a good régime has been established, to omit all treatment other than blood pressure reduction without recurrence of heart failure. Here is a paradox—we much prefer to receive a heart failure patient with a blood pressure of 250/140 to one of say 160/90. The reason is that with the higher pressure the heart failure is almost certainly of a removable cause, whereas . . . less amenable to treatment . . . failure."

Sieber, Grimson and Orgain (1953) have treated 46 patients by

pentapyrrolidinium at 8 a.m., 2 p.m. and 10 p.m. respectively. The highest dose reached by Smirk (1953b) was 70 mg. twice daily (in polyvinyl pyrrolidone solution). Smirk has found that both hexamethonium bromide and pentapyrrolidinium dissolved in 25 per cent. polyvinyl pyrrolidone give more prolonged effects, so that two injections a day may suffice. Rosenheim (1954) finds polyvinyl pyrrolidone does not effect response or excretion.

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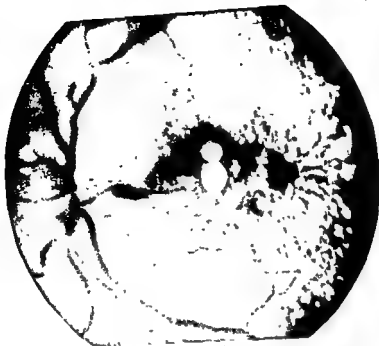


FIG 15 1.



FIG 15 2

hexamethonium salts by mouth, three patients with these substances parenterally and one by combined therapy. They obtained good control during in-patient treatment in 40 per cent., during the first four months of out-patient treatment in 16 per cent., and during the subsequent five to nineteen months in 6 per cent. of patients. They noticed frequent amelioration of hypertensive symptoms, occasional decrease in retinopathy and improvement in the electrocardiogram and heart size.

The experience of many clinics, including our own, now demonstrates conclusively that adequate control of arterial pressure by methonium compounds causes the regression of hypertensive neuro-retinopathy and the prolongation of life, provided that treatment is begun before renal or cardiac involvement has progressed too far. Figs. 15.1 and 15.2 reproduce photographs of the fundus oculi (Platt, 1954b) from a boy aged 13 whose blood pressure on admission was 220/170, for which no renal or adrenal cause was found. Fig. 15.1 shows the left fundus in May, 1952, at the beginning of treatment. Fig. 15.2, in September, 1953, subcutaneous hexamethonium bromide having been used in the interval. The conspicuous resolution of papilloedema and retinal exudates is obvious and is illustrative of Platt's more general experience, with which mine agrees.

Complications of Treatment

Two general points should be emphasized. First, sensitivity to hexamethonium and pentapyrrolidinium varies, and it is always wise to start with a small dose. Should intravenous treatment be required, the arterial pressure should be measured during and after the injection. A profound fall of arterial pressure may require the use of methedrine (2.5 to 30 mg. subcutaneously or intravenously) or an infusion of nor-adrenaline (5 mg. per litre of saline given at a rate of 2 to 20 μ g per minute). Second, these drugs are largely excreted in the urine and their action may be greatly prolonged in patients whose renal function is impaired.

Treatment with the methonium compounds has some potentially serious and some minor but disturbing complications. These are:

Major Complications of Methonium Therapy

(a) *Complications which are Due to the Hypertensive Disease.* Fatal coronary occlusion (Sieber and others, 1953) and strokes (Smirk and others, 1954) have been reported during methonium therapy. Coronary occlusion occurred during treatment in four of our patients. Coronary thrombosis and cerebral vascular accidents are frequent without any treatment. *Angina pectoris* is usually regarded as a

contraindication to methonium; and so little is known of how patients with angina respond to treatment. From what we know of the pathogenesis of anginal pain and of cerebral vascular disturbances, it is not surprising that patients may develop anginal pain or transient hemiparesis at the height of the fall of arterial pressure (Morrow and others, 1953). In some of our patients, such incidents have made control of arterial pressure difficult. Advanced renal failure usually progresses, probably because the kidney has been nearly completely destroyed by the time therapy begins.

(b) *Complications due to the Action of Methonium.* (1) Loss of consciousness, especially on standing, is the result of overdosage and is aggravated by other hypotensive situations. For instance, one of our patients on oral treatment developed diarrhoea; each time he got hurriedly out of bed to relieve himself, he fell to the ground unconscious. This symptom merely requires rest in the horizontal posture and reduction in the dosage of the drug. Occasionally, injection of methedrine, or noradrenaline infusions may be needed.

(2) Interference with bowel action is usually no more than constipation, best relieved by a daily laxative. But it may progress to something very much simulating intestinal obstruction; in fact, in one patient I saw, exploratory laparotomy was undertaken with subsequently fatal results. Morrow and others (1953) also record a case, operated on for complete obstruction, in which recovery took place. So far as is known, these cases will always recover if the drug is stopped, if laxatives are given and if dehydration is prevented by intravenous infusion. Carbachol (carbamyl chloride) is worthy of trial. There is little doubt that the daily administration of laxatives (e.g. cascara) and, should the patient get grossly distended with gas, the occasional omission of a dose or several doses, are usually adequate to counteract any untoward bowel symptoms.

In one patient with incomplete pyloric obstruction due to peptic ulceration, vomiting was so troublesome that treatment with hexamethonium had to be discontinued (Morrow and others, 1953).

(3) Interference with micturition is rarely important—but it may be in those with prostatic hypertrophy, and it may be necessary to remove the prostate before treatment can be continued (Morrow and others, 1953). If retention is troublesome, omission of a dose will allow the bladder to be emptied. Carbachol may rarely be necessary.

(4) Eustachian duct obstruction

...initial pulmonary oedema has been described by Morrison (1953). It has been described also by Morrow and others (1953) in patients receiving combined hexamethonium and

the progress and complications of localized vascular disease of the coronary and cerebral arteries is affected beneficially, adversely, or not at all is problematical. Terminal renal failure cannot be reversed, and it should be remembered in the treatment of those patients in whom the kidneys are damaged, that hexamethonium is excreted largely by glomerular filtration, and that the excretion of these substances is therefore unduly prolonged.

HYDRALLAZINE (L-HYDRAZINOPHTHALAZINE, APRESOLINE)

This substance was discovered during an investigation into anti-malarial compounds. It has the peculiar property of decreasing arterial pressure, while increasing renal and femoral blood flow in dog and rabbit. It has a wide range of action, the nature of which has not yet been fully elucidated.

Intravenous injection of 0.25 to 0.5 mg. per kg. in man produces a fall in diastolic pressure and, in hypertensive subjects, a fall in systolic pressure with an increase in renal blood flow (40 per cent.) and of cardiac output (110 per cent.), but no change in skin temperature. Intra-arterial apresoline caused an increase in skin temperature (Wilkinson and others, 1952). It increases renal blood flow, whether or not the arterial pressure falls, while the glomerular filtration rate remains unchanged or falls, an effect attributed to afferent glomerular arteriole dilatation. The cerebral blood flow remains unchanged. The ECG may show transient ST depression and T wave inversion found most often in lead V_2 (Freis and Finnerty, 1950). Most of the patients showing these changes already have hypertensive or ischaemic abnormalities on the ECG. The changes are attributed to increased cardiac output without increased coronary flow and are said to be prevented by hexamethonium (Moyer, 1953).

After an intravenous dose of 0.25 to 0.5 mg. per kg. in man, the arterial pressure begins to fall in five to twenty minutes, reaches a minimum in twenty to ninety minutes, and may remain at this level for one and a half to four hours. It slowly returns to its original level in four to eight hours.

Hydrallazine reduces arterial pressure when given by mouth, and has been used in the treatment of hypertension by Taylor and others (1952, 1954). Schroeder (1952a) treated 50 patients with hypertension and succeeded in lowering diastolic pressure by 20 mm. or more, but, in only a few of the mildest cases were normal values achieved.

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a ... mg. doses or to a total of 800 mg. daily. One-fourth of the patients responded by decreases in diastolic arterial pressure to normal, and one-third by

hydrallazine therapy, particularly in negro men. I have had one typical case in a man with chronic nephritis treated with hexamethonium. The condition can be recognized at a glance. The patient is extremely breathless with very fast respiration, and the breathlessness, unlike any other condition with which I am acquainted, is *much worse when the patient sits up*. The treatment of such cases is controversial. Some recover and some die if the drug is continued.

Minor Complications are :

(a) Dry mouth and loss of appetite which may be relieved by chewing gum or 0.25 mg. carbachol given in chloroform water before meals.

(b) Blurred vision due to paralysis of accommodation, which is best counteracted by new spectacles, when the dose has been finally adjusted, or by 1 per cent. *eserine eye drops*.

(c) Diminution in libido and potency can also be temporarily relieved by omission of one or two doses.

Comment. The methonium compounds, in my experience, offer by far the most promising therapy that has been introduced for hypertension. But their use makes the most exacting demands on the physician and patient. To use them successfully the physician must have faith in them, and know how to help his patient over the difficulties their use involves. The patient must be sufficiently aware of the gravity of his (or her) condition to tolerate the discomforts, have sufficient morale to persevere, and sufficient intelligence to adjust his way of life to the changes in behaviour which the use of these drugs entails. These considerations explain the very varying results that have been reported (see Pickering, 1952a).

Clearly the methonium compounds should not be used in patients who are symptomless, unless their arterial pressure is bordering on the malignant level (a diastolic of 130 or over in patients under 40, 140 or over above this age is a fair guide). Clearly also the drugs should be used energetically and without delay in patients in the malignant phase, whatever the underlying lesion, whether or not it has been established if the cause is removable, and whether or not the kidneys are involved, provided only that the patient is not in terminal renal failure; meanwhile steps are taken to ascertain if there is a removable cause. Clearly the drugs should be used in those with left ventricular failure as early and energetically as possible. Cardiac failure of the congestive type would seem to be beneficially affected. Between these limits of symptomless hypertension, on the one hand, and of the supervention of the malignant phase or of congestive cardiac or left ventricular failure on the other, there is a no-man's-land about which only a guess can be made until the situation is clarified by a proper clinical trial. Whether

nium and hydralazine was possible, one was partly and seven were completely relieved, while one other stopped treatment. Three of Harris and Turner's (1954) patients who received only hydralazine had angina; in none were the symptoms convincingly aggravated.

RAUWOLFIA SERPENTINA

Extracts of this Indian plant were found by Bhatia (1942) to have a hypotensive action, and have been recently extensively used in man, particularly by Wilkins and Löffler (for references see Doyle and Smirk, 1954). Several preparations are available of the crude root, mixed alkaloids and of a single alkaloid, reserpine. The mode of action of the drug is not known. Doyle and Smirk found that large doses (2 to 3 mg. reserpine thrice daily) by mouth sometimes produced striking falls of blood pressure, at times to normal levels, beginning after four to six hours, and lasting sometimes for more than twelve hours after withdrawing the drug. Postural hypotension was unusual. These doses produced conspicuous side-effects, such as flushing, conjunctival and nasal congestion, fatigue, sleepiness and depression, and are therefore unsuitable for routine administration. With the doses ordinarily advocated (0.75 to 1.5 mg. daily) both side-effects and hypotensive effects were equally mild; but, occasionally, satisfactory

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initiate therapy on hypertension in almost every case in which treatment is deemed necessary, unless the condition of the patient makes it imperative that blood pressure be reduced at once. If Rauwolfia itself is ineffective, subsequent control of the hypertension may be possible with smaller doses of a more potent agent, thereby reducing or eliminating side-effects. Smirk, Doyle and McQueen (1954) have found that the use of reserpine improves the degree of control that can be obtained with pentapyrrolidinium by mouth, allowing the use of smaller doses and diminishing the side-effects.

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decreases to diastolic levels less than 110 mm. Hg. Cerebrovascular disease showed most improvement; nephrosclerosis ceased to progress and renal function sometimes increased; cardiac function showed little improvement and in some deteriorated. Harris and Turner (1954) gave a critical review of the action of the substance and of previous experience. They treated 22 patients and succeeded in getting good control of arterial pressure in 18 cases during the first ten days using daily doses up to 1,200 mg. After this period the dose required to produce the same response gradually increased and in many cases the effect was ultimately lost. Side effects and toxic reactions were very common and were the main reason for stopping treatment in 18 patients. While they diminished with continued treatment, so did the blood pressure effect, and control of blood pressure by increase of dose was usually regained at the price of a return to the side effects. They concluded, and I think, on the evidence, fairly, that hydrallazine by itself has no place in the treatment of hypertension, though, as we shall see in the next section, it can be used most effectively with hexamethonium.

The toxic and side effects have been fully discussed by Morrow and others (1953); Dustan and others (1954); and by Harris and Turner (1954), and are perhaps the chief objection to the use of the drug. They include headache, flushing of the skin, palpitations and throbbing head, œdema of the skin, weakness, apathy, drowsiness, blurred vision, paræsthesiæ, dry mouth, nausea and vomiting and arthralgia, all of which may occur early and may disappear with continued administration of the drug. More important are severe febrile reactions which may make it impossible to continue. In 17 of the 258 patients treated by Morrow and others, with hydrallazine and hexamethonium (1953), a condition resembling acute rheumatoid arthritis and disseminated lupus occurred four to twenty-three months after beginning therapy. Multiple arthritis was the outstanding manifestation, and skin rashes, hepatomegaly and abnormal thymol turbidity, pyrexia, high erythrocyte sedimentation rate, anaemia, leucopenia, adenopathy, splenomegaly and hæmaturia were less constant. The incidence, when they wrote, was increasing. Regression towards normal always followed cessation of the drug. Dustan and others (1954) recorded one patient who was able to resume hydrallazine therapy after eighteen months and tolerate 250 mg. daily without return of joint pain. With this exception, all patients had recurrence of the rheumatic state when treatment was reinstated. Kaufman (1953) recorded a case of pancytopenia recovering two weeks after stopping the drug.

In the series reported by Morrow and others (1953) hydrallazine increased anginal pain in two and was discontinued after a few doses. In nine other patients with angina in which a prolonged trial of metho-

Schroeder and others (1953) have reported the use of hexamethonium combined with hydrallazine in 258 patients treated for six to twenty five months. Eighty-nine patients were in the malignant phase, of whom five were in terminal uræmia, and 130 had severe benign hypertension. The arterial pressure fell in all and was maintained at a reasonable level in 80 per cent. The malignant phase was alleviated in all, but only three-quarters survived. The limiting factor in the effectiveness of the treatment was renal insufficiency.

Our experience has confirmed the value of the addition of hydralazine to methonium salts for the control of arterial pressure. It seems that Rauwolfia used with pentapyrrolidinium offers, at the present time, the most effective control with the minimum of evil consequences.

TREATMENT OF THE COMPLICATIONS OF HYPERTENSION

The following account will be brief, since the treatment of these conditions will be found in works on general medicine and therapeutics.

(1) *Congestive cardiac failure* is treated in the ordinary way with digitalis, mercurial diuretics and a low sodium diet. It often reacts well to successful blood pressure control by hexamethonium or sympathectomy. From its action it might be suspected that hydralazine should not be used.

Management of myocardial infarction. An intravenous injection of aminophylline (0.25 to 0.5 g.) and oxygen may be given if necessary. Hexamethonium bromide injected slowly, intravenously, in doses of 5 to 15 mg. according to the response of the arterial pressure, is often quickly effective. Digoxin 1 mg. intravenously may help. The attacks are prevented by adequate blood pressure control, which is imperative.

(3) *Cerebral haemorrhage or thrombosis* usually requires no treatment other than antibiotics, good nursing and the institution of re-educative measures, early in thrombosis, and later in haemorrhage. Blood pressure control by hexamethonium is desirable immediately after the attack in haemorrhage, but not in thrombosis, and subsequently, certainly in haemorrhage, and probably in thrombosis.

(4) *Hypertensive fits* (eclamptic attacks, acute pseudouræmia, acute hypertensive encephalopathy), should not be treated by lumbar puncture, which, in my experience, is ineffective. They are said to react well to intravenous hexamethonium salts, 5 to 15 mg. according to the effect on arterial pressure. Subsequent blood pressure control is imperative.

(5) Angina pectoris and coronary thrombosis are treated in the ordinary way by nitrites and ...

adding pentapyrrolidinium if necessary. Freis (1954) has recorded four cases of depression following long use of reserpine, relieved in three by stopping the drug.

COMBINATIONS OF THERAPIES PARTICULARLY METHONIUM COMPOUNDS AND HYDRALLAZINE OR RAUWOLFIA

Many of the blood pressure reducing measures have been used in combination to obtain enhanced effects. A low sodium diet is often used in combination with methonium salts and veratrum compounds. However, the most potent combination would seem to be between hydrallazine or Rauwolfia and the methonium compounds. The first combination was tried because it was noted that hydrallazine produced a much larger fall in arterial pressure in patients with hypertension who had previously had a sympathectomy than in those who had not. This treatment has been used particularly by Schroeder (1952b) who gives hexamethonium chloride by mouth eight-hourly to produce a fluctuating blood pressure that falls to normal values and then rises again. Hydrallazine is then begun in doses of 25 to 50 mg. every eight hours and increased to 100 mg. every four hours or until the arterial pressure is persistently normal. The arterial pressure is measured before each dose, which is adjusted so that the full dose of hexamethonium is taken if the arterial pressure exceeds 140 systolic, half the dose if it lies between 130 and 140, and quarter the dose if the pressure lies between 120 and 130, and none if the systolic pressure is below 120 mm. Hg. A member of the patient's family is taught to estimate the arterial pressure. Of 20 patients with benign hypertension, 14 were successfully controlled. Of 15 patients with malignant hypertension, four had their blood pressures maintained at normal levels, and in all but two the pressure was kept as low as 160/100. The malignant phase was reversed in 13. Unsuccessful sympathectomy was controlled with greater difficulty by hydrallazine because of postural hypotension. It was necessary to maintain these patients' blood pressures in the supine position between 160 and 170 systolic. Schroeder did not observe focal cerebral effects. Angina seemed to be precipitated in two patients in whom the arterial pressure was reduced by hydrallazine, but was relieved in another. Renal insufficiency was precipitated in one patient owing to too low an arterial pressure. Four patients with malignant and three with benign hypertension omitted to take the drugs; of these three were recontrolled, two continued to take the drugs sporadically and two gave up. Freis and others (1952) treated 14 patients with malignant hypertension with hexamethonium salts; six had a remission and this was induced in four others with hydrallazine; four patients, three of whom had advanced renal failure, did not respond. More recently,

begun at once. In patients with hypertensive fits the drug should be given intravenously. In the remainder the drug may be begun by

the patient experiences faintness

(once daily) is begun at the same

time as the pentapyrrolidinium. Satisfactory control may require the pentapyrrolidinium being given thrice daily, or the evening dose being doubled, or the drug being given subcutaneously. In some cases the substitution of hydralazine for reserpine allows control. Should the patient be too stupid or unco-operative for this therapy, or should he or she loathe (as some do) such an exacting regime, sympathectomy should be considered. Its success is greatest in young subjects and many, in whom it is at first successful, later require drug therapy.

(4) Patients in whom arterial pressure should probably be lowered, but in whom there is no urgency, include symptomless patients whose pressures are thought to be so high that the pressure endangers life, or those with angina

daily), the dose being reduced to 0.5 mg. twice daily as soon as it becomes prominent. In a very few patients this alone controls arterial pressure in about three weeks. If, after this time, control is not secured, begin to add pentapyrrolidinium and continue to increase the dose, as outlined in the preceding paragraph, until control is achieved.

(5) Patients requiring no specific therapy are in general those without symptoms, or those whose symptoms are not due to hypertensive cardiovascular disease, provided their pressures are not high enough seriously to endanger life.

The division between this and the previous category is arbitrary, and the doctor must use his common sense, knowing the effect of different blood pressure levels and different complications of high pressure on prognosis, and forecasting, as he can, the probable reaction of his patients to the therapy employed. It will be many years before exact knowledge is gained as to whether lowering blood pressure with those drugs does in fact improve prognosis in symptomless patients, or indeed in those with cerebral or coronary disease. On general grounds it may be suspected that hypotensive drugs will be relatively useless in any patient with a diastolic pressure persistently below 100 mm. Hg; and that they will prove increasingly effective the more the arterial pressure exceeds this value.

(6) In all cases the doctor should have a frank discussion of the situation with the patient, and endeavour to remove the patient's fears (some of which may be only too well grounded). The doctor should always avoid frightening the patient, particularly when

uncertain whether these conditions are beneficially or adversely affected by blood pressure control.

(6) *Uræmia* is usually terminal in hypertension and in my view the kindest treatment is to make the patient comfortable by heroin or other similar measure. In acute nephritis, however, this is not so and the matter will receive further notice in Chapter 16. If there is reasonable doubt as to the cause of uræmia, it must, of course, be treated, in case the cause is transient or removable.

(7) *Rupture of aorta and formation of dissecting aneurysm* is not usually amenable to specific therapy, but requires good nursing and attention to those details which indicate whether danger is arising from heart failure, blood loss or failure of circulation to a particular part.

SUMMARY

SUGGESTED PROCEDURE IN THE MANAGEMENT OF A PATIENT WITH HIGH BLOOD PRESSURE

On the evidence available at the time of writing (November, 1954) the following seems the best outline of how to manage patients with high blood pressure :

(1) Decide whether the high blood pressure is secondary or, by excluding a recognized cause, essential. Diagnosis is discussed in detail in Chapter 24. If the hypertension is secondary, can, or should, the underlying lesion be removed ? If a progressive disease is present, can it be arrested ?

(2) In all cases of essential hypertension, and in those with secondary hypertension where the cause cannot be removed, or where hypertension persists after removal of the cause, a decision must be taken whether or not to lower blood pressure. Patients can be divided into three groups :

- (a) Patients in whom there is an urgent indication to lower arterial pressure.
- (b) Patients in whom arterial pressure should be lowered, but there is no urgency.
- (c) Patients in whom there is no indication to reduce arterial pressure.

(3) Patients in whom there is an urgent need to lower arterial pressure include those having hypertensive fits ; those with left ventricular failure or congestive heart failure and gross hypertension ; and those in the malignant phase. In all such patients blood pressure must be reduced at once, even though a removable cause for hypertension has not yet been excluded ; if found, this can be removed later. In such cases energetic treatment with pentapyrrolidinium should be

begun at once. In patients with hypertensive fits the drug should be begun by ~~intravenous~~ In the remainder the drug may be begun by ~~intravenous~~ and twelve hours later. An patient experiences faintness on standing. Reserpine (0.5 mg. thrice daily) is begun at the same time as the pentapyrrolidinium. Satisfactory control may require the pentapyrrolidinium being given thrice daily, or the evening dose being doubled, or the drug being given subcutaneously. In some cases the substitution of hydralazine for reserpine allows control. Should the patient be too stupid or unco-operative for this therapy, or should he or she loathe (as some do) such an exacting regime, sympathectomy should be considered. Its success is greatest in young subjects and many, in whom it is at first successful, later require drug therapy.

(4) Patients in whom arterial pressure should probably be lowered, but in whom there is no urgency, include symptomless patients whose pressures are thought to be so high that the pressure endangers life, those with cardiac symptoms and enlargement, those with angina pectoris and those having a past history of a cardiac or cerebral vascular accident. Such patients may be started on reserpine (0.5 mg. thrice daily), the dose being reduced to 0.5 mg. twice daily if side-effects become prominent. In a very few patients this alone controls arterial pressure in about three weeks. If, after this time, control is not secured, begin to add pentapyrrolidinium and continue to increase the dose, as outlined in the preceding paragraph, until control is achieved.

(5) Patients requiring no specific therapy are in general those without symptoms, or those whose symptoms are not due to hypertensive cardiovascular disease, provided their pressures are not high enough seriously to endanger life.

The division between this and the previous category is arbitrary, and the doctor must use his common sense, knowing the effect of different blood pressure levels and different complications of high pressure on prognosis, and forecasting, as he can, the probable reaction of his patients to the therapy employed. It will be many years before exact knowledge is gained as to whether lowering blood pressure with those drugs does in fact improve prognosis in symptomless patients, or indeed in those with cerebral or coronary disease. On general grounds it may be suspected that hypotensive drugs will be relatively useless in any patient with a diastolic pressure persistently below 100 mm Hg, and that they will prove increasingly effective the more the arterial pressure exceeds this value.

(6) In all cases the doctor should have a frank discussion of the situation with the patient, and endeavour to remove the patient's fears (some of which may be only too well grounded). The doctor should always avoid frightening the patient, particularly when the

doctor himself is faced with a very difficult situation, as, for example, whether or not to remove an apparently abnormal kidney. In such cases the available information should be sought, the best opinion obtained and the patient advised accordingly. This may all seem very unnecessary advice, but my experience leads me to suppose that it cannot be stressed too much.

CHAPTER 16

NEPHRITIS AND NEPHROSIS

NEPHRITIS

NEPHRITIS played a most important part in the development of our knowledge and ideas concerning high arterial pressure. It was the condition observed and described by Bright; the similarity between its terminal stages and those of the malignant phase of essential hypertension did much to delay the recognition of the latter; and the prominence of high blood pressure as a manifestation of nephritis led Tigerstedt and Bergman to seek and find renin. A vast literature has grown up on nephritis which has been reviewed by Van Slyke and others (1930), Volhard (1931), Fishberg (1939) and Addis (1948). Here we are chiefly concerned with its relationship to hypertension, but before proceeding to this we may discuss briefly the natural history of the disease, its morbid anatomy and its aetiology.

THE NATURAL HISTORY AND CLASSIFICATION OF NEPHRITIS

Bright's (1836c) description of the natural history of the disease is so graphic and succinct that it is worth quoting in its entirety:

"A child, or an adult, is affected with scarlatina, or some other acute disease; or has indulged in the intemperate use of ardent spirits for a series of months or years: he is exposed to some casual cause or habitual source of suppressed perspiration: he finds the secretion of his urine greatly increased, or he discovers that it is tinged with blood; or, without having made any such observation, he awakes in the morning with his face swollen, or his ankles puffy, or his hands oedematous. If he happen, in this condition, to fall under the care of a practitioner who suspects the nature of his disease, it is found, that already his urine contains a notable quantity of albumen: his pulse is full and hard, his skin dry, he has often headache, and sometimes a sense of weight or pain across the loins. Under treatment more or less active, or sometimes without any treatment, the more obvious and distressing of these symptoms disappear, the swelling, whether casual or constant, is no longer observed; the urine ceases to evince any admixture of red particles; and, according to the degree of importance which has been attached to these symptoms, they are gradually lost sight of, or are absolutely forgotten. Nevertheless, from time to time the countenance becomes bloated; the skin is dry; headaches occur with unusual frequency, or the calls to micturition disturb the night's

repose. After a time, the healthy colour of the countenance fades ; a sense of weakness or pain in the loins increases ; headaches, often accompanied by vomiting, add greatly to the general want of comfort ; and a sense of lassitude, of weariness, and of depression, gradually steal over the bodily and mental frame. Again the assistance of medicine is sought. If the nature of the disease is suspected, the urine is carefully tested ; and found, in almost every trial, to contain albumen, while the quantity of urea is gradually diminishing. If, in the attempt to give relief to the oppression of the system, blood is drawn, it is often buffed, or the serum is milky and opaque ; and nice analysis will frequently detect a great deficiency of albumen, and sometimes manifest indications of the presence of urea. If the disease is not suspected, the liver, the stomach, or the brain divide the care of the practitioner, sometimes drawing him away entirely from the more important seat of disease. The swelling increases and decreases ; the mind grows cheerful, or is sad ; the secretions of the kidney or the skin are augmented or diminished, sometimes in alternate ratio, sometimes without apparent relation. Again the patient is restored to tolerable health ; again he enters on his active duties : or he is, perhaps, less fortunate ;—the swelling increases, the urine becomes scanty, the powers of life seem to yield, the lungs become oedematous, and, in a state of asphyxia or coma, he sinks into the grave ; or a sudden effusion of serum into the glottis closes the passages of the air, and brings on a more sudden dissolution. Should he, however, have resumed the avocations of life, he is usually subject to constant recurrence of his symptoms ; or again, almost dismissing the recollection of his ailment, he is suddenly seized with an acute attack of pericarditis, or with a still more acute attack of peritonitis, which, without any renewed warning, deprives him, in eight and forty hours, of his life. Should he escape this danger likewise, other perils await him ; his headaches have been observed to become more frequent ; his stomach more deranged ; his vision indistinct ; his hearing depraved : he is suddenly seized with a convulsive fit, and becomes blind. He struggles through the attack ; but again and again it returns ; and before a day or a week has elapsed, worn out by convulsions, or overwhelmed by coma, the painful history of his disease is closed.”

The clinical features of Bright's disease are largely composed of alterations in the volume and composition of the urine, œdema, hypertension and renal failure. Each of these provides a provoking problem and, since these features may present themselves in various combinations which may succeed each other in great variety, the disease has proved a paradise for the medical taxonomist. In fact, the literature over the past century has been largely dominated by the problem of classification. Fortunately, that subject is beyond our

scope in this work and it will suffice to base the following clinical description on that of Longcope (1936) and of Ellis (1942)¹ who pointed out that the course of the disease might follow two patterns named, respectively, Types A and B and Types I and II. Type I nephritis corresponds fairly clearly with the hæmorrhagic nephritis of Addis; less closely with the glomerulonephritis of Volhard and Fahr (1914) and Volhard (1931). Type II nephritis corresponds fairly well with the degenerative nephritis of Addis (1928); and with the nephrotic stage of nephritis (Fishberg, 1939), less closely with nephrosis.

TYPE A NEPHRITIS OF LONGCOPE. TYPE I NEPHRITIS OF ELLIS

Type I nephritis is essentially a disease of children and young adults, 80 per cent. of Ellis's cases belonging to the first two decades of age. Classically, the disease begins with an attack of what used to be called acute diffuse nephritis, ten to thirty days after a sore throat or other infection. The patient notices swelling of the face, hands, ankles or feet. Or he may notice that his urine is bloody. Malaise, headache and vomiting, pain in the loins and abdomen are less common and striking complaints. Breathlessness, particularly on exertion, was one of the most striking features of acute nephritis of World War I but is less noticeable in the acute nephritis of peace-time; but I have seen it as the presenting symptom. On examination, the patient presents slight pitting œdema which is quite generalized, affecting face, backs of forearms and hands, trunk and legs, but is rarely severe. The arterial pressure is usually moderately raised, particularly the systolic value, and there is often a small rise of venous pressure that can be detected in the neck veins.

The urine is usually, seen on microscopy, particularly if the hourly rate of excretion is low.

It is usually, of a pale, turbid, or bloody color, with a sedimentation rate of 0.15 and an orthochromic anemia.

As the condition may get worse, urine being very scanty and containing much blood; œdema, hypertension and nitrogen retention progress. More commonly, however,

¹ Ellis makes no reference to Longcope's classification. Presumably, the two authors arrived independently at the same conclusion.

soon after the patient is put to bed, the urine output increases, the amount of blood in it diminishes, œdema and hypertension disappear.

Complications of Acute Stage

In the patients who get worse the following complications may occur :

- (a) Complete suppression of urine with increasing œdema, hypertension and renal failure. This is probably best treated by the regime described by Borst (1948) and by Bull, Joeckes and Lowe (1949). The patient receives no protein, and enough calories, water and electrolytes to balance his loss. The latter authors gave one litre of water containing 100 g. peanut oil and 400 g. glucose daily. It is now known that frequent estimations of plasma sodium and potassium are essential so that these ions may be given as required.

The artificial kidney is less successful in the hands of most.

- (b) Acute heart failure with pulmonary œdema, which should be treated by restriction of fluid and sodium intake, methonium salts and full digitalization (remembering that digitalis and methonium salts are excreted in the urine).
- (c) Hypertensive fits, which occurred in 6.4 per cent. of Ellis's patients in the acute phase. They have no effect on the ultimate prognosis.
- (d) Infection—the original infection, or a new infection, such as bronchopneumonia.

Course

The course of acute nephritis may be divided into four types.

- (1) *Recovery.* This occurred in 85 per cent. of Longcope's and 82 per cent. of Ellis's cases, but has been less common in other series, perhaps because Type II cases have been included. Recovery may begin at varying times from the onset, and complete recovery may occur in patients who have had anuria, who have had very high blood ureas, who have had hypertensive fits, heart failure and hypertensive neuro-retinopathy. The volume of urine rises so that there is a good diuresis; œdema disappears; the arterial pressure falls, blood urea falls, protein and red cells diminish in the urine. Protein commonly disappears from the urine before red cells, and a slight excess of red cells may persist for some weeks after all other abnormalities have gone. They eventually disappear also. The time from onset to complete disappearance of proteinuria may vary from a few weeks to about three months, or, exceptionally, twelve to twenty-four months.
- (2) *Death in the acute phase* occurred in 4 per cent. of Ellis's cases.

Three patients died of the preceding infection, three of uræmia and one of heart failure.

(3) *Rapidly progressive course* (subacute type of Volhard, stormy type of Loehlein) occurred in 4 per cent. of Ellis's cases, admitted with less than two weeks' history. In these, the oedema, hæmaturia and hypertension persist, and indeed become accentuated. Renal function progressively deteriorates and, without any subsidence of symptoms, the patient dies with hypertension and uræmia, within weeks or months from the onset of the disease.

(4) *Recovery to the latent stage, followed Months or Years later by the Terminal Picture of Chronic Nephritis.* In these patients the course is towards recovery, but protein and red cells never disappear entirely from the urine, even though the patient is apparently quite well, has no cedema, a normal blood pressure, and normal renal function to the ordinary tests. Ten per cent. of Ellis's patients with acute nephritis had persistent proteinuria. These patients may die up to twenty-five years after the acute attack. In the terminal phase, they present a clinical picture closely resembling the terminal picture of malignant essential hypertension characterized by gross hypertension, gross enlargement of the left ventricle, often with heart failure of the congestive or left ventricular type, hypertensive neuro-retinopathy, cerebral hæmorrhage or thrombosis, and uræmia. The commonest cause of death is uræmia, the next cerebral hæmorrhage, and the third cardiac failure.

Between the first and the last stages, the rate and mode of progress of the disease is very variable. At one extreme is the vascular type of nephritis of Volhard, in which there is a moderate hypertension,

benign essential hypertension. In such patients the clinical condition may stay unchanged for years and the only clear distinction from benign essential hypertension may be the past history of acute nephritis. At the other is the repeated appearance of gross hæmaturia, each bout followed by a decline in renal function and rise in arterial pressure, the terminal phase being reached in a few months to a few years. The onset, to the red cells.

It is extremely probable that at least ten per cent. of the cases concerned in hypertension; but Acute infection, are apt to be followed by a terminal hæmaturia and a decline of renal function.

vascular lesion found in essential hypertension, except those reflecting the effects of ageing. The acute fibrinoid arteriolar necroses that characterize the malignant phase are found in those patients with acute nephritis and the moderately elevated pressures, that are the highest observed in the acute phase; necroses are also found in those patients with chronic nephritis who have the highest pressures. It seems probable, therefore, that in these patients, at least, the vascular lesions of the malignant phase must add their not inconsiderable quota to the destruction of the patient.

Morbid Anatomy

In the acute phase the kidney is pale and tense but shows little other macroscopic abnormality. Microscopically, the characteristic lesion is in the glomerular tuft, which is swollen and empty of blood, with swollen endothelial cells and an increase in the number of polymorphs and red cells in Bowman's capsule and the tubules (Fig. 16.1). In some cases, fibrinoid necrosis of the afferent arterioles and of the glomeruli may be seen, similar to the lesions found in the malignant phase of other types of hypertension. Fishberg (1927) found acute arteriolar necroses of the vasa afferentia in three of eight

is shrunken and granular, the depressed portions representing areas in which the renal substance has been destroyed and replaced by fibrous tissue, the raised portions collections of hypertrophied nephrons with enlarged glomeruli and dilated tubules (Fig. 16.3). Vascular changes are intense, particularly intimal proliferation and, often, arteriolar necroses. The features which most clearly distinguish this kidney from that of the malignant phase of essential hypertension are the gross reduction in the total number of glomeruli, and rarity of unaltered glomeruli. Some of these show acute necrosis, others increased cellularity, loss of lobulation of the tuft and extensive capsular adhesions with pericapsular fibrosis.

The vascular changes in other organs are similar to those found in essential hypertension, except in so far as the degenerative lesions of the media, and atheroma, are uncommon in children and young adults, who are the chief victims of Type I nephritis.

Acute Focal Nephritis

In the course of certain acute infections as, for example, acute tonsillitis, the patient may have protein, casts and blood in the urine, the blood being, sometimes, visible to the naked eye. Hypertension and œdema are absent. Recovery from the renal lesion is complete

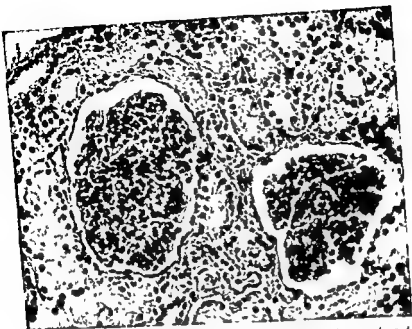


FIG 16 1 (250) ACUTE TYPE I NEPHRITIS The glomeruli are enlarged, ischaemic and excessively cellular From a girl of seven who died of pulmonary oedema ten days after the onset of acute nephritis (Dr K Porter)



FIG 16 2 (, 350) RAPIDLY PROGRESSIVE FORM OF TYPE I NEPHRITIS Showing a crescent made up of proliferated epithelial cells From a male aged 20 who died six weeks after the onset, with extreme oliguria and infarction of lungs Blood urea 400 mg per 100 ml, B P. 180/90 (Dr K Porter)

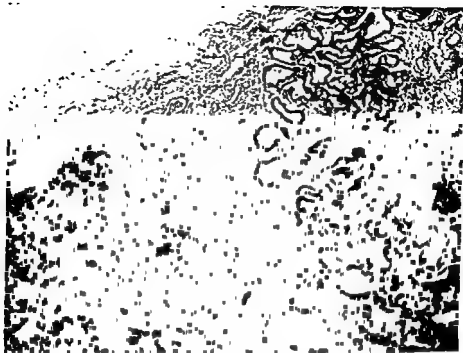


FIG. 16.3 ($\times 250$) TYPE II NEPHRITIS. The glomerulus shows diffuse thickening of the capillary basement membrane. (Dr. H. Porter.)

years after the discovery of proteinuria at routine examination. (Dr. H. Porter.)

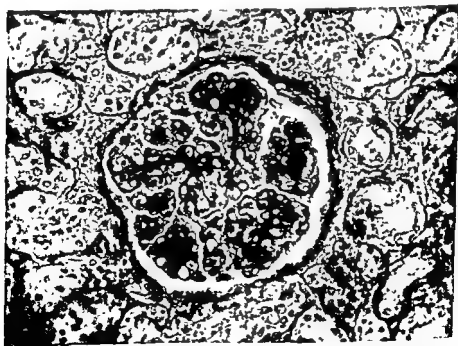


FIG. 16.4 ($\times 250$) TYPE II NEPHRITIS. The glomerulus shows diffuse thickening of the capillary basement membrane. From a male aged 45 years with proteinuria and edema.

in a few days to a few weeks. In patients who die of their infection, the kidney shows acute focal lesions.

TYPE B NEPHRITIS OF LONGCOPE. TYPE II NEPHRITIS OF ELLIS

Type II nephritis is a disease of insidious onset, affecting all ages, although half begin between the ages of 10 and 30, and is dominated by oedema, at least in its early stages. Recovery is the exception. There is usually no notable antecedent infection. Swelling is the first, and often the only, symptom. It begins in the face, scrotum or feet and often quickly becomes severe, affecting all parts, but particularly the feet. On examination two abnormalities are found: oedema which may be gross and in some cases accompanied by ascites and hydrothorax, and proteinuria, also usually gross, the excretion of protein varying from 1 to 30 g. per day. There is often no nitrogen retention and the concentrating power of the urine is usually normal. Some cases show no hypertension, others a mild or moderate increase. The deposit often shows fatty casts and oval fat bodies, and frequently an excess of red and white cells, but macroscopic hæmaturia is rare. The blood may show a slight anaemia, increased sedimentation rate, normal urea, a diminished protein content and often a greatly increased blood cholesterol, one of the findings which led to the naming of some of these cases "hypoid nephrosis." The chief complication in the early stages is infection. The serous cavities and the skin are always prone to infection, but particularly when attempts are made to drain the fluid mechanically; bronchopneumonia also occurs. Antibiotics have reduced this risk. Sometimes an acute infection, such as measles or pneumonia, is followed by a massive diuresis with disappearance of oedema.

The oedema in this condition is probably due to hypoproteinaemia. Van Slyke and his colleagues (1930) showed that it occurs when the total serum protein is below 5.2 to 5.8 g. per 100 ml. and the albumin below 2.3 to 2.8 g. per 100 ml. The colloid osmotic pressure of plasma is chiefly due to the smaller molecule, albumin, which contributes 7.54 cm. H_2O per g., the larger molecule, globulin, contributing only 1.95 cm. H_2O per g. per 100 ml (Govaerts 1927). The increase in the

incre:

both

larger molecule, globulin, correlating with the greater diminution of albumin in the plasma. Eighty-five per cent. or more of the urinary protein is albumin (Hiller, McIntosh and Van Slyke, 1927), but the other fractions also appear in the urine.

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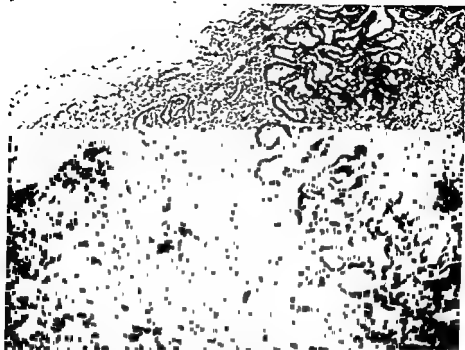


FIG. 16.3 ($\times 60$) CHRONIC TYPE I NEPHRITIS. Showing thickened adherent renal capsule, glomeruli in various stages of fibrous obliteration, interstitial fibrosis and tubular hyperplasia, dilatation and atrophy. From a male aged 37 who died of uraemia with hypertension in the malignant phase three years after the discovery of proteinuria at routine examination. (Dr. K. Porter)

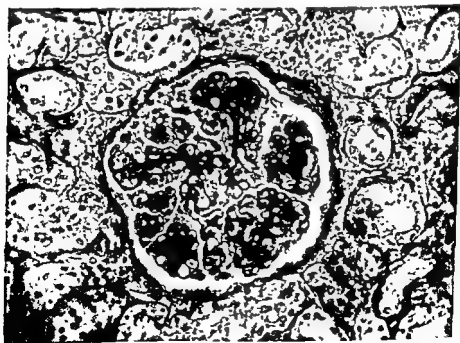


FIG. 16.4 ($\times 250$) TYPE II NEPHRITIS. The glomerulus shows diffuse thickening of the capillary basement membrane. From a male aged 36 who died of bronchopneumonia two years after onset of oedema

in a few days to a few weeks. In patients who die of their infection, the kidney shows acute focal lesions.

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As might be expected, the relationship between proteinuria, hypoproteinæmia and œdema is not quite simple. Linder, Lundsgaard and Van Slyke (1924) showed that, while there was a rough quantitative

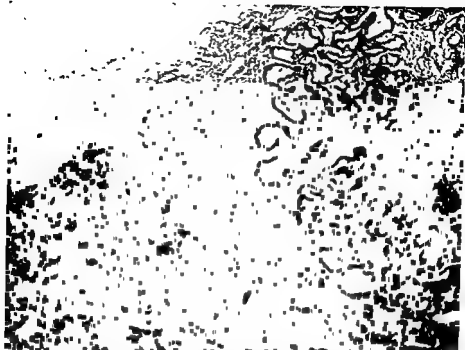


FIG 16.3 ($\times 60$). CHRONIC TYPE I NEPHRITIS Showing thickened adherent renal capsule, glomeruli in various stages of fibrous obliteration, interstitial fibrosis and tubular hyperplasia, dilatation and atrophy. From a male aged 37 who died of uræmia with hypertension in the malignant phase three years after the discovery of proteinuria at routine examination. (Dr. K. Porter.)



FIG. 16.4 ($\times 250$). TYPE II NEPHRITIS. The glomerulus shows diffuse thickening of the capillary basement membrane. From a male aged 36 who died of bronchopneumonia two years after onset of œdema. Periodic Acid Schiff Stain (Dr. K. Porter)

in a few days to a few weeks. In patients who die of their infection, the kidney shows acute focal lesions.

TYPE B NEPHRITIS OF LONGCOPE. TYPE II NEPHRITIS OF ELLIS

Type II nephritis is a disease of insidious onset, affecting all ages, although half begin between the ages of 10 and 30, and is dominated by oedema, at least in its early stages. Recovery is the exception. There is usually no notable antecedent infection. Swelling is the first, and often the only, symptom. It begins in the face, scrotum or feet and often quickly becomes severe, affecting all parts, but particularly the feet. On examination two abnormalities are found: oedema which may be gross and in some cases accompanied by ascites and hydrothorax, and proteinuria, also usually gross, the excretion of protein varying from 1 to 30 g. per day. There is often no nitrogen retention and the concentrating power of the urine is usually normal. Some cases show no hypertension, others a mild or moderate increase. The deposit often shows fatty casts and oval fat bodies, and frequently an excess of red and white cells, but macroscopic haematuria is rare. The blood may show a slight anaemia, increased sedimentation rate, normal urea, a diminished protein content and often a greatly increased blood cholesterol, one of the findings which led to the naming of some of these cases "lipoid nephrosis". The chief complication in the early stages is infection. The serous cavities and the skin are always prone to infection, but particularly when attempts are made to drain the fluid mechanically, bronchopneumonia also occurs. Antibiotics have reduced this risk. Sometimes an acute infection, such as measles or pneumonia, is followed by a massive diuresis with disappearance of oedema.

The oedema in this condition is probably due to hypoproteinaemia. Van Slyke and his colleagues (1936) showed that it occurs when the total serum protein is below 5.2 to 5.8 g. per 100 ml. and the albumin below 2.3 to 2.8 g. per 100 ml. The colloid osmotic pressure of plasma is chiefly due to the smaller molecule, albumin, which contributes 7.54 cm. H₂O per g., the larger molecule, globulin, contributing only 1.95 cm. H₂O per g. per 100 ml. (Goyaerts 1927). The haematocrit is low, and both

albumin and globulin, is lost more freely than the larger molecule, globulin, correlating with the greater diminution of albumin in the plasma. Eighty-five per cent. or more of the urinary protein is albumin (Hiller, McIntosh and Van Slyke, 1927), but the other fractions also appear in the urine.

As might be expected, the relationship between proteinuria, hypoproteinaemia and oedema is not quite simple. Linder, Lundsgaard and Van Slyke (1924) showed that, while there was a rough quantitative

correlation between protein loss in the urine and hypoproteinæmia, there were exceptions ; some patients, with much heavier proteinuria than others, having higher plasma proteins. Presumably an additional nutritional factor is concerned. For a given hypoproteinæmia, œdema is greatly influenced by the sodium intake. When the plasma protein is very low, œdema usually never disappears entirely. When, however, the plasma protein is borderline, œdema may come and go for no obvious reason (Van Slyke and others, 1930).

In Ellis's series of 145 cases there were nine in which the urine was examined before the onset of œdema. In these, protein was found five years, three years, one year (two cases) and between six and one month (four cases) before the occurrence of œdema. Thus the disease begins some time before it presents with its first symptom.

Type II nephritis may follow either of two courses. A very few (five of 145 cases of Ellis) recover apparently completely. It is quite possible that these cases belong to a completely different category ; three of Ellis's cases had no hypertension and they would, therefore, correspond to what has been called "genuine nephrosis." The more usual course of Type II nephritis is continuous and progressive and, in this, it contrasts sharply with Type I. This occurred in the remainder of Ellis's cases and all of Longcope's 25. (Edema may persist or may remit and relapse. The best guide to progress is the blood pressure, since this correlates fairly well with the state and progress of renal impairment. In the cases in which the arterial pressure is high in the early stages, the course is rapidly progressive to death in renal failure within one to five years of the outset ; œdema is persistent or recurrent, but usually disappears (apart from terminal heart failure) in the later stages, as the blood pressure rises further and renal failure develops. The final phase presents a picture closely similar to the end stages of progressive Type I nephritis and malignant essential hypertension, characterized by gross hypertension, cardiac enlargement, hypertensive neuro-retinopathy, and renal insufficiency. Death occurs from uræmia, cerebral hæmorrhage or heart failure. The cases in which the blood pressure is moderately high follow a similar but slower course. Alternatively, the arterial pressure may return to normal and the disease runs an even more chronic course, such as is seen when the blood pressure is initially normal. In such cases, œdema is the dominant feature and death often occurs from infection ; or it may come and go over many years until, finally, hypertension and renal failure complete the picture.

Morbid Anatomy

In the exceptional cases dying early in the disease, the kidneys show the very slight changes described in nephrosis, that is to say, glomerular

thickening of the basement membrane of the tufts (Fig. 16.4) and lipid infiltration of the tubules. In the larger group, dying with hypertension and oedema within five years of onset, the kidneys are usually enlarged and pale in colour (the large white kidney). The chief lesion is in the glomeruli which are enlarged and show a uniform lesion, the chief feature of which is focal deposition of hyaline material at the centre of the lobules of the glomerular tuft. The tubules are infiltrated with fat and lipid to a varying extent. In some cases the lipid content is so high as to make the cut surface greasy. In still more chronic cases there is an even more advanced degree of glomerular hyalinization which affects all the glomeruli more or less equally, so that even when death occurs after some ten years, the kidney shows no great contraction and there is not the great reduction in the number of glomeruli that is characteristic of Type I nephritis. Vascular and glomerular lesions of the hypertensive type are much less frequently seen and interstitial fibrosis is diffuse rather than focal.

TREATMENT OF NEPHRITIS

Type A Nephritis of Longcope. Type I of Ellis

When the acute disease is recognized the patient should be put to bed at once and kept warm. Volhard (1931) recommends a hunger and thirst cure, that is, the patient is starved of food and drink for two days followed by two cups of weak tea and a little fruit daily for two or three more days. This has been successful in my hands, but neither I nor anyone else, to my knowledge, has any controls. Others use a diet of about 1,500 cals. containing 20 to 25 g. protein.

If the patient recovers from the acute phase, he can be regarded as healthy. The chief problem in patients in the latent and chronic stages is to protect from infection. The patient should certainly spend as little time in hospital as possible, and, so far as is compatible with economic and social factors, he should avoid exposure to wet, to extremes of temperature and to crowds, particularly in enclosed spaces. The persistent daily administration of prophylactic doses of sulpho-

nasal sinuses. Winkenwerder, McLeod and Baker (1935) comparing an operated and a control series, found "that elimination of foci of infection apparently did not prevent either postoperative infections or exacerbations of nephritis, since the average number of each was greater in the operative than in the nonoperative cases." Later in the disease hypertension will require control by the methods described

in Chapter 15; sympathectomy may give results at least as good as in essential hypertension; and the hexamethonium salts will prove increasingly useful. It should be remembered that while the indications for, and aims of, treatment designed to lower arterial pressure are much the same in essential hypertension and chronic nephritis, less satisfactory results may be anticipated in nephritis, where there is an additional underlying progressive disease.

Addis (1948) has given reasons why the protein content of the diet should be limited throughout the course of Type I nephritis. It should, of course, be limited in the terminal stages, when renal function is greatly impaired.

Type B Nephritis of Longcope. Type II of Ellis

While the rôle of infection in this condition is more doubtful, it is the general practice to protect the patient so far as possible. Should an infection occur, antibiotics should be used energetically since infection is so often the cause of death. Paradoxically, an attack of measles may be followed by a diuresis and prolonged remission.

In the stage characterized by œdema, restriction of sodium intake and a high protein diet are used to limit œdema and prevent gross protein depletion of the body (Squire, 1953). Albumin and dextran infusions may clear the œdema temporarily. More striking results have been obtained by ACTH and cortisone. Luetscher and Deming (1950) obtained diuresis, loss of œdema and diminution of proteinuria from cortisone (0.5 to 2.1 gm. over five to sixteen days) in six of 11 patients with the nephrotic syndrome. The remission lasted days to months. Similar results have been obtained by many others. The usual doses employed are 75 to 100 mg. ACTH daily or 50 mg. in young children; and 300 mg. cortisone and 200 mg. in young children. The dosage is maintained for five to fourteen days and abruptly withdrawn, since diuresis is most apt to occur just after cessation of the therapy. If the result is unsatisfactory, second and third courses may be given after five days' interval. When diuresis occurs, proteinuria usually diminishes and may vanish and the plasma proteins return towards normal. The remissions may last for weeks. It is not yet known if any are permanent. The chief dangers during and after administration of ACTH or cortisone are severe hypertension and sodium and potassium depletion. Estimations of plasma sodium and potassium are, therefore, important.

Mersalyl will often disperse œdema when other measures have failed. In my experience, it does not adversely affect the kidney.

ÆTIOLOGY OF NEPHRITIS

Observations on Man

That acute nephritis frequently begins after infection was, as we have seen, apparent to Bright. Infection is related to nephritis in three ways; acute focal nephritis occurs during an acute infection when fever is high; acute diffuse nephritis usually occurs about two weeks after the onset of an acute infection; and trench nephritis, or war nephritis of World War I, appeared to occur in epidemics but without an antecedent history of infection (MacLean, 1919). Acute focal nephritis concerns us no further, and the following account will be largely devoted to acute diffuse nephritis (Type I nephritis).

In the past century the commonest antecedent infection was scarlet fever, nephritis occurring somewhere between the tenth and thirtieth day. With the decline in the severity of scarlatina, nephritis has followed it less frequently, and it has become more usual to obtain a history of other types of infection. Longcope (1929), Ellis (1942), Brod (1949) and Addis (1948) give lists of these infections, which agree

between less than a week and more than three weeks, and averages about seventeen days. It is generally agreed that the streptococcus causes scarlet fever. In Longcope's (1929) series of 48 cases of nephritis a β -haemolytic streptococcus was isolated from the associated infected tissue in three, and an α -haemolytic streptococcus in seven. Streptococci were, however, very rarely obtainable from urine, kidney or blood, and, because of this and because of the similarity between the latent period and that of serum sickness, he therefore supposed, as Schick (1907) and von Pirquet (1911) had before, that nephritis was an allergic manifestation. In keeping with this hypothesis, he found that filtrates of streptococcal cultures gave very strong skin reactions in 23 per cent. of controls, 18 per cent. of patients who had tonsillitis and 67 per cent. of patients with nephritis. The hypothesis that nephritis is, in some way, a manifestation of an antigen-antibody reaction receives support from the fall in serum complement in Kelleff and

nephritis

Lange and

in all cases of acute and chronic progressive nephritis, and in most cases of the nephrotic stage. Longcope (1936) found high antistreptolysin titres regularly in his Type A nephritis. In his Type B the antistreptolysin titres were rarely above normal and were in some cases extremely low. Rammelkamp and Weaver (1953) found Lancefield Type 12 streptococci in 25 of 31

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after an interval of eight days to three weeks from the first injection. However, Humphrey (1948) was unable to confirm their observations using black and white hooded rats.

Fahr (1936), in reviewing the work of Masugi and others of his pupils, recorded their complete failure to produce acute diffuse nephritis in rabbits with streptococcal toxins with numerous adjuvant measures such as cold, adrenaline, previous sensitization or diphtheria toxin. In Masugi's rabbits, acute diffuse nephritis closely resembled acute diffuse nephritis of man; some failed to heal, showing polyuria and rise of blood pressure and resembled human contracted kidney with hypertrophy of the heart. The kidney vessels were dilated and not contracted in the early stages, thus offering no support for Volhard's hypothesis that the changes of acute nephritis were due to vascular spasm.

The concept of hypersensitization as a cause of nephritis is, in certain respects, extremely nebulous, since it is by no means clear what the antigen would be or how it would be related to streptococci in human disease. The most prevalent idea is of auto-immunization to partly modified host-proteins.

Comment It would seem quite possible that, in the two types of nephritis described, we are dealing with two diseases of rather different aetiology, although there is some overlap. In Type A of Longcope or Type I of Ellis, an acute infection nearly always precedes the onset, antistreptolysin titre is high and complement reduced; a comparable disease in animals may be produced by a mechanism involving an antigen-antibody reaction.

obtained from rabbits into rats, particularly of the Long-Evans strain produces changes which are similar to those of the Long-Evans strain of Type II nephritis.

HYPERTENSION IN NEPHRITIS

Acute Nephritis

It is in accordance with this hypothesis, namely, that in acute nephritis hypertension precedes albuminuria. This very important observation, which is generally overlooked in contemporary accounts of the disease, is generally overlooked by Hen-

¹ Perle
record that the copy produced for me in the Radcliffe Science Library of the University of Oxford in February 1954 was uncut.

patients with *acute nephritis*. They considered that the variations in the incidence of nephritis following scarlet fever are due to variations in the nephritis producing capacities of the infecting organisms.

War nephritis in World War I was not usually preceded by an acute infection. It seemed to occur more frequently in British than Belgian or French troops, and in epidemics in particular units, the epidemic continuing for some time after the unit was at rest. Infection was generally regarded as the cause but all attempts to recover a causal organism failed (MacLean, 1919).

Observations on Animals

Numerous attempts have been made to reproduce lesions resembling those in human acute and chronic nephritis by bacterial toxins and procedures in which an antigen antibody reaction is concerned. Masugi (1933) was the first to succeed. He washed rat kidney or liver free of blood, emulsified them and injected the emulsions daily into rabbits for five to sixteen days. The resultant antisera were injected into the tail veins of rats. Specific lesions were found within twenty-four hours. The chief lesions were in the kidney, where they resembled human acute nephritis and in the liver, resembling eclampsia. The anti-liver serum produced less change in the kidney than in the liver, and the anti-kidney serum produced less change in the liver than in the kidney. He got similar results using rabbits by preparing an anti-serum in ducks. In rabbits the only lesions produced by the anti-kidney serum were in the kidneys. When the dose was small the lesions were focal, and the urine contained red cells and casts but there was no hypertension. With larger doses the nephritis was diffuse, and associated with hypertension and nitrogen retention. The rise of blood pressure was noted to precede the urinary changes by two to three days and to last a few days to several months, according to the severity of the lesion (Masugi, 1934). *Edema was inconspicuous and rather doubtful*. These observations have been repeated, confirmed and amplified. Smadel (1936) showed that the nephrotoxin is most readily obtained by immunization with kidney suspensions, but may occasionally appear after injections of other organ preparations, except erythrocytes and serum; it may be removed by adsorption on kidney cells or less readily on liver cells. That the response is not quite tissue specific is suggested by Seegal and Loeb (1946), who obtained chronic glomerulonephritis in 18 of 32 rats injected with rabbit anti-rat-placenta serum.

Much more relevant to the phenomena of human disease appeared the papers of Cavelti and Cavelti (1945), claiming that mixtures of killed group A streptococci and emulsion of rat kidney would, when injected intraperitoneally in rats, either as a single dose or as four to ten separate doses, produce acute nephritis closely resembling that of man

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HYPERTENSION IN NEPHRITIS

Acute Nephritis

It is commonly held that hypertension is a secondary phenomenon to the renal lesion. The established fact is, however,

namely, that in acute nephritis hypertension precedes albuminuria. This very important observation, which is generally overlooked in contemporary accounts of the disease, was first described independently by Henoch (1873) and by Mahomed (1874) in his oft quoted paper on

¹ Perhaps many of those who quote this paper have not read it. I am pleased to record that the copy produced for me in the Radcliffe Science Library of the University of Oxford in February 1954 was correct.

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resultants of a generalized vascular reaction of an allergic type. Hypertension would result from generalized vasoconstriction or swelling of the vessel walls; œdema from increased capillary permeability, and the renal lesion from swelling of the endothelium of the capillaries of the glomerular tuft, and increase in their permeability and fragility. This hypothesis would account for the time relations of the three components and for the fact that, very occasionally, patients exhibit œdema and hypertension without any manifest renal changes (Brod, 1949).

Hypertension and œdema in acute nephritis were often found in war nephritis to be associated with hydræmia, i.e. a low hæmoglobin and a high water content of the blood, and it was found that the three changes usually declined together, though sometimes there was a discrepancy between them (MacLean, 1919).

In cases of acute nephritis, Davies (1951) found the cardiac output, measured by cardiac catheterization, to be in the upper normal range, though the venous pressure was slightly elevated in all. The heart, in fact, behaved as though it were in an early stage of failure. As the arterial pressure fell, so did the venous pressure. Since cardiac output is not increased and since blood viscosity tends to be reduced (Pickering, 1936c), hypertension is almost certainly due to vascular narrowing. The conditions of blood flow have been studied in only two tissues, the hand and the kidney. In the hand, I found that blood flow, after releasing vasomotor nervous tone, was in the upper normal range or above it, in six patients with acute nephritis and hypertension. In four of these the blood flow fell *pari passu* with the arterial pressure; and the slopes of the lines relating blood flow and diastolic pressure were approximately parallel to one another in the four patients, and in a patient with arteriovenous fistula, in whom arterial pressure could be altered passively by compressing the artery proximal to the fistula. It seemed clear, therefore, that there was no evidence for any non-nervous vasoconstriction in the hand vessels in the acute phase; acute nephritis contrasting sharply in this respect with chronic nephritis and essential hypertension. These observations were confirmed by Arnott and Matthew (1939).

The renal circulation has been studied by Earle, Taggart and Shannon (1944) and Black and others (1948) using the clearance methods of Smith. All clearances are reduced, but the inulin more than the diodone, suggesting that the main increase of resistance affects the afferent vessel.

One point seems abundantly clear from these observations; that the behaviour of the circulation through hand and kidney is so different in acute nephritis and in essential hypertension, as to leave little doubt that the mechanism of hypertension is also very different in the two diseases.

the "pre-albuminuric stage of Bright's disease." Mahomed gauged the arterial pressure by the characteristics of the pulse tracing and by the weight that had to be applied to the sphygmograph to develop the pulse tracing to its greatest extent. In this paper he was concerned with acute nephritis following scarlet fever. He wrote: "The observations I have now to bring before you are briefly these: 1st. That previous to the commencement of any kidney change, or to the appearance of albumen in the urine, the first condition observable is high tension in the arterial system. . . . The series of cases to which I especially desire to draw your attention this evening are all of one type. Their characteristic features are these: They all occur in patients recovering from scarlet fever." He then described seven cases in which the observation had been made.

The next observation on this subject was made by Nonnenbruch (1917), who found that in war nephritis in the German army, the arterial pressure was raised in about two-thirds of cases, but the rise often lasted only a few days. It could precede urinary abnormalities and was therefore due to a general vascular, and not to a renal, change. Kylin (1921) described three patients with sore throat in whom a rise of arterial pressure preceded by several days the appearance of albumen, blood and casts, in the urine. Koch (1926) found that, in scarlet fever patients, it was common to find red cells and casts in the urine with a trace of œdema but no hypertension in the acute phase. At the fourteenth to twentieth day a rise of blood pressure was not uncommon, but might occur in only one or two daily measurements or might last several days; erythrocytes and albumin were usually found in the urine when the blood pressure was raised. The rise of arterial pressure preceded the urinary abnormalities. Steiner (1928) thought the urinary changes preceded the hypertension after scarlet fever. Bayart (1933), however, confirmed Koch's findings in 232 cases of scarlet fever. There was no rise of blood pressure in 133. In 94 the blood pressure rose between the tenth and thirtieth day (mean seventeenth); in 80 of them there was no urinary abnormality; in the remainder, albumin, with or without red cells and casts, appeared in the urine at the same time as, or following, the rise of blood pressure. In five cases, albuminuria occurred without a rise of blood pressure.

Nonnenbruch (1917) noted that the œdema fluid in acute nephritis was clear, and contained 1.5 per cent. protein, as contrasted with the milky fluid of the nephrotic stage, containing only a trace of protein. He thought the œdema was also extrarenal. Kylin (1926) made the same observation and suggested that hypertension and œdema were both due to widespread vascular damage. It is, in fact, a very tempting hypothesis that the three essential components of acute nephritis, hypertension, œdema and the renal lesion are the three

Van Slyke and others (1930) could find no exact relationship between the course of the renal lesion in hemorrhagic nephritis and the blood pressure. Thus a seven-year-old girl developed hypertension (200 mm. Hg) while a normal urea excreting power was maintained. On the other hand, in a patient proceeding from the acute to the active chronic state, no hypertension developed in at least a year during which the renal lesions showed a steadily downward course. They noted that, in exceptional cases, hemorrhagic nephritis can run its entire course

... tantalizingly slight. Nor have we much evidence on which to base any clear conception as to the nature of the circulatory fault. Renin would seem to be a possible agent, but the evidence is again tantalizingly slight and confused. Dexter and Haynes (1944) report finding increased amounts of renin in the blood in three cases of eclampsia and one of acute glomerulonephritis (no details). They state "In cases of preeclampsia and acute glomerulonephritis with only moderate elevation of blood pressure or where the hypertension has been of gradual onset, and in patients with chronic hypertension with pressures as high as 285 systolic and 180 diastolic, we have been unable to detect renin in the systemic blood." Braun-Menendez and others (1946) merely state, in reference to acute nephritis, "renin has actually been detected in the systemic blood of two patients in which it was investigated by us."

Effect of Hypertension on the Course of Nephritis

Hypertension is probably closely correlated with two of the complications of the acute stage of Type I nephritis, namely cardiac failure and hypertensive fits. In the acute phase, insufficient time has elapsed for cardiac hypertrophy, and the heart seems to tolerate much lower pressures than in a sustained hypertension. Measures to lower arterial pressure, particularly using the methonium drugs, therefore seem indicated. Arteriolar necroses occur in the kidneys in the acute phase, and although published reports suggest that they occur at lower pressures than in sustained hypertension, and the nephritis process itself may be a factor in their production, yet there is at least a case for supposing that the level of arterial pressure may be a factor, and, therefore, for reducing arterial pressure in the acute phase, if the diastolic rises, say, above 110 mm. Hg. In the chronic phase the anatomical consequences of hypertension are the same.

Chronic Nephritis

Comparatively little attention has been given to the circulation in chronic nephritis using modern methods. The older methods (see Braun-Menendez and others, 1946) suggest that cardiac output is normal, but it may rise in the terminal phases when anaemia becomes profound. The blood viscosity is normal or decreased (Pickering, 1936b).

Calorimetric estimations of hand blood flow, after release of vasomotor nervous tone, revealed a precisely similar situation to that in essential hypertension, namely a persistence of vascular narrowing (Pickering, 1936b). In one case of progressive chronic nephritis, a rise of blood pressure was accompanied by a fall in hand blood flow measured under these conditions (Pickering, 1943). Thus the rise of blood pressure was accompanied by an increase in the non-nervous vasoconstriction in the hand. These observations suggest strongly that the increased peripheral resistance in chronic nephritic hypertension is not of vasomotor nervous origin.

The circulation through the kidney in various stages of nephritis has been studied by Earle, Taggart and Shannon (1944) using the mannitol, inulin and diodone clearance methods. Their 22 patients were in varying stages of both Type I and Type II nephritis but only a few had hypertension. They found that the advance of the disease was associated with a progressive depression of the renal plasma flow (diodone clearance), the glomerular filtration rate (mannitol clearance) and the mass of functional tubular tissue (diodone Tm). Interestingly enough glomerular filtration rate is relatively more depressed than renal plasma flow, giving a reduced filtration fraction in all except a few cases in the chronic phase with hypertension; this may, perhaps, be correlated with the dominant position occupied by glomerular changes in the pathological anatomy of the condition. It is, in fact, extremely difficult to draw any conclusions concerning the functional state of the renal circulation in nephritis, since the results are so greatly affected by the gross anatomical lesions present.

There seem to be no figures available for the blood flow through other tissues of the body. Although our evidence is very incomplete, it suggests that the circulation in chronic nephritis is rather similar to that in essential hypertension except for the kidney where the position is complicated by the pronounced local lesions. From time to time it has been stated that the behaviour of the blood pressure to certain stimuli in chronic nephritis differs from the behaviour in essential hypertension, but our attempts to verify such statements showed either no significant difference, or differences that could be attributed to age (Pickering and Kissin, 1936; Pickering, 1936b).

injured muscle cells. These pigments pass the glomerulus and are converted into acid hæmatin in the distal tubules when the urine becomes acidified. Clinically, the onset is heralded by anuria or oliguria. The urine usually contains protein and, in most of the conditions listed, it contains dissolved pigment, giving a positive guaiac reaction, and appropriate absorption bands for myoglobin or hæmoglobin and masses of pigment casts composed of acid hæmatin. The phase of oliguria or anuria may last a few days to three weeks. Then the urine output rises slowly or quickly, often to over 1 or 2 litres a day. At first the urine is almost an ultrafiltrate of plasma, differing not at all in urea content, slightly in sodium and potassium and usually lacking in glucose. Later, the concentrations of urea and creatinine rise and the concentrations of sodium and potassium fall, and the kidney slowly regains its selective concentrating power. In some cases it returns apparently to normal in three to nine months. During the acute phase, renal blood flow and oxygen consumption are greatly reduced, later regaining normal values.

The arterial pressure is not usually raised in these cases. It would be interesting to know whether hypertension develops much later, ■■ seems to be the case with toxæmia of pregnancy.

(2) "*Genuine Nephrosis*" may be defined as characterized clinically by hypercholesterolaemia, proteinuria, cylindruria, and oedema, and by the absence of hæmatina, urea retention and hypertension; and histologically by the absence of gross glomerular lesions, though the chief abnormality, namely, the lipid inclusions in the tubules, probably results from tubular reabsorption of substances that have passed through the abnormally permeable, and abnormally thick, basement membranes of the glomerular loops. Most of these cases eventually prove to be in an early phase of type 2 nephritis. But in a very few cases the characteristic features of nephritis are absent throughout and the condition cures itself spontaneously, after weeks or months, without hypertension having developed.

(3) *Amyloid Nephrosis* Amyloidosis is a complication of prolonged infections, such as tuberculosis, sepsis and syphilis, but, occasionally, complicates other chronic febrile states such as rheumatoid arthritis and psoriasis. It is now becoming rare. Amyloid is deposited in many organs, including liver and spleen, which are often easily felt *per abdomen*. In the kidney the deposits occupy the glomeruli and the blood vessels, and are associated with tubular atrophy and later replacement fibrosis, giving a contracted kidney, not unlike that of chronic nephritis, at first sight. In the early stages, proteinuria may be the sole evidence of renal involvement. Later, protein loss may be so great as to lower the plasma proteins to a level at which oedema results and, thereafter, oedema is the predominant feature. As the kidney

in others with very high pressures the malignant course may be followed. That the clinical features of the end stages of the malignant phase of essential hypertension, and of Types I and II nephritis, are indistinguishable is no accident, since, according to the thesis presented here, at this stage in all three conditions, the outstanding features are the consequences of a hypertension of great intensity. The case for controlling arterial pressure by methonium compounds or otherwise in chronic nephritis is as cogent as in essential hypertension.

HYPERTENSION IN THE SO-CALLED "NEPHROSES"

In 1905 Friedrich Muller introduced the term "nephrosis" to describe those affections of the kidney that were primarily degenerative rather than inflammatory. Neither the concept nor the definition have ever been entirely satisfactory, partly at least because the term "degenerative" is itself incapable of exact definition and delimitation. The conditions described from time to time under the term nephrosis have been so obscure in ætiology, and ill-defined in their clinical features, that a vast literature has grown on this fertile soil; for this the reader is referred to the works of Volhard (1931) and Fishberg (1954). Here, the more important varieties will be described only very briefly.

(1) *Acute Tubular Necrosis* (Lower Nephron Nephrosis). This condition has been studied in detail by Bull, Joeke and Lowe (1950) It may result from the following causes :

- (a) poisons, particularly mercury, but including bismuth, gold, arsenobenzol, lysol, and carbon tetrachloride.
- (b) Obstetrical mishaps, particularly concealed accidental hæmorrhage and obstructed labour.
- (c) Incompatible transfusion.
- (d) The "crush syndrome."
- (e) Blackwater fever.
- (f) Burns.
- (g) Wounds, operations and other agents producing prolonged low blood pressure (shock).

The underlying lesion is a necrosis of the tubules, particularly the collecting tubule, second convoluted tubule and the ascending limb of Henle's loop. In addition, the collecting tubules are frequently obstructed by pigment casts. Three factors may be concerned in its pathogenesis, poisoning of the cells, as by mercury, obstruction of the collecting tubules by hæmatin casts, and prolonged renal ischaemia due to prolonged low arterial pressure. Hæmatin casts are a notable feature in mismatched transfusion and blackwater fever, in which the plasma contains hæmoglobin derived from lysed red cells, and in the crush syndrome in which myoglobin is liberated into the plasma from the

contains large amounts of albumin and there is usually impairment of concentrating power with or without nitrogen retention." Newburger and Peters in 1939 described four more cases thoroughly studied both in life and after death; all had diabetes, albuminuria, hypertension and retinitis: the diabetes was mild requiring no insulin for its control. Siegal and Allen (1941) sought to discover to what extent the lesion was peculiar to diabetes. In 100 consecutive post-mortem examinations in cases without diabetes, no lesion of this type was found; in 100 consecutive cases with hypertension but without diabetes, one case was observed, a 51-year-old female, whose arterial pressure was 160/90 and who had a retinopathy compatible also with diabetic retinopathy. In 100 consecutive cases of diabetes, 40 and over, the

approximately described a group of 11 cases of: — for picture and diabetics, an which was, indeed, found in an advanced stage in four of these patients who died. They noted that the diabetes was mild, requiring little or no insulin for

many years before the albuminuria, but in two, renal symptoms and signs developed a few months before diabetes was discovered. Three patients had peripheral neuritis. All had elevated arterial pressures ranging from 180/90 to 220/140, the latter patient

TABLE 16.1. *Comparison of Necropsy Findings in Diabetic Patients who had Inter-capillary Glomerulosclerosis with those who had not.*

Data from Henderson, Sprague and Wagener, 1947.

	Kimmelstiel-Wilson lesion present	Kimmelstiel-Wilson lesion absent
Average age, years	60	59
Incidence of hypertension (SBP 150 or more)	60 per cent.	32 per cent.
Incidence of cardiac decompensation	33	11
Incidence of oedema	47	19
Decreased foot pulses	51	22
Gangrene	13	4
Diabetic neuropathy	23	5
Diabetic retinopathy	68.8	22.8
Raised blood urea	64	53
Death from cardiovascular disease	52.5	30.1

substance is destroyed and replaced by fibrous tissue, renal function begins to fail, polyuria ensues and eventually uræmia. In this late stage hypertension may occur, but is seldom gross, and very rarely severe enough to enter the malignant phase. The comparatively low incidence and low intensity of hypertension in this form of contracted kidney is no doubt to be ascribed to the causal infective disease, since as we have seen, infection and fever, in general, reduce the intensity of hypertension.

(4) *Bence-Jones Protein Kidney.* In those cases of multiple myeloma and other growths in the bone-marrow in which Bence-Jones Protein is excreted in the urine, the kidney may, in long-standing cases, become contracted, with renal failure; hypertension is present in some, but in by no means all, cases. The contracted kidney is probably the result of tubular destruction following tubular occlusion by precipitated protein (Bell, 1933).

THE DIABETIC KIDNEY AND DIABETIC RETINOPATHY

Since patients suffering from diabetes have been enabled, through insulin, to survive for many years, a rather striking clinical syndrome has emerged, and now provides one of the commonest findings in subjects with diabetes of many years' duration. The syndrome has two components, a renal and a retinal lesion, which are sometimes found separately but are most often combined. A nervous lesion is also often present.

The Diabetic Kidney

The renal lesion was first described by Kimmelstiel and Wilson in 1936 under the name intercapillary glomerulosclerosis. The typical lesion was a mass of hyaline material appearing in the centre of the glomerulus or in the centre of a lobule and deposited in the intercapillary connective tissue (Fig. 16.5). Nearly all glomeruli were so affected. The tubules showed extensive fatty degeneration and lipoid was frequently found in the interstitial tissue. Arteriosclerosis was present, usually of very high degree, fatty degeneration of the arterioles being unusually conspicuous. Grossly the kidneys "present the picture of arteriosclerotic contraction which may be in part or completely obscured by the signs of nephrosis, i.e. they may be enlarged and swollen with grayish or yellowish external and cut surfaces." "The clinical picture appears . . . to be almost as characteristic as the histological one: the patients are relatively old; hypertension is present, usually of the benign type, and the kidneys frequently show signs of decompensation; there is a history of diabetes usually of long standing; the presenting symptoms may be those of edema of the nephrotic type, renal decompensation or heart failure; the urine

Loewenstein (1943) and of Ashton (1951), we now know that many of the round "haemorrhages" are in fact microaneurysms of the retinal venules and that these are the earliest and probably basal component of the lesion. Ashton (1951) has reported the results of examining *post mortem* 110 diabetic subjects including the eyes. Retinopathy was present in 68 per cent, Kimmelstiel-Wilson's disease in 36 per cent. The best results were obtained in the eye, by injecting the artery with a red and the vein with a black dye. This showed clearly that microaneurysms varying in size from 20 to 30 μ , that is, the limit of ophthalmoscopic visibility, to 75 to 100 μ are situated on the venules, and not on the arterioles (Fig. 16.7). Sometimes these aneurysms leak, giving the characteristic round haemorrhage, having the appearance of a small sponge. Sometimes they leak muco-protein and fat giving retinal exudates (Fig. 16.8). No microaneurysms were found in any other organ except the kidney, and Ashton believes that microaneurysm formation on the glomerular tufts (Fig. 16.6), and subsequent leakage of muco-protein is the basis of the Kimmelstiel-Wilson lesion as it is of the retinopathy. A close relationship was observed between the intensity of the two lesions. Thus, of 18 cases with the mildest retinopathy, only one had the glomerular lesion and that was moderate. Of 17 cases with severe retinopathy, eight had severe, three moderate and five mild, and only one no, glomerular lesion.

Ballantyne and Lowenstein (1943) found that 60 per cent. of diabetics with retinal lesions had normal blood pressure. Scott's figures (1951) were similar, 68 of 150 cases had blood pressure below 140/90.

into

pat

11 per cent from those who had had diabetes for less than one year, to 73 per cent. in those who had diabetes for longer than twenty years. It is not however, as has himself had

Wilson, Root

... result in poor control of diabetes, and state in reference to young subjects that they have never seen the renal lesion develop in a long-standing case in which the diabetes has been efficiently controlled. Others, such as Lawrence, are not so impressed with the influence of adequate diabetic control. Allen (1941), Friedewald (1948) and Ashton (1949, 1953) have shown that the hyaline deposits in the glomeruli and the waxy deposits in the retina are similar in showing an affinity for aniline blue, lamination with silver nitrate, and stain red with the periodic acid Schiff (PAS) method. It is probable, therefore, that the deposits contain polysaccharide and

having a "clinical course so accelerated as to suggest the possibility of malignant hypertension." Ten of the 11 had eyeground changes, eight of the 11 cardiac decompensation, and 10 cases had nitrogen retention, progressing to uræmia in six. Seven of the 11 cases died within two to three years after the onset of the renal syndrome, death being due to uræmia, cardiac failure, or both. Henderson, Sprague and Wagener (1947) found that the Kimmelstiel-Wilson lesion was not specific for diabetes, being found in 19.5 per cent. of 313 diabetics, 12.3 per cent. of 81 chronic nephritics and 5.2 per cent. of 134 cases of hypertension. The incidence of associated lesions in diabetic patients with and without the lesion is shown in Table 16.1.

Although the Kimmelstiel-Wilson lesion is thus most frequently found in elderly diabetics, it has become increasingly frequent in young people who have had diabetes for over ten years. Wilson, Root and Marble (1951) point out that diabetic nephropathy is now responsible for more deaths than any other single cause in young patients with severe, poorly controlled diabetes of long duration, while, before 1937, only 2 per cent. of deaths in such subjects were due to renal disease. They reviewed 247 patients whose diabetes had begun between the ages of eighteen months and thirty years and had been present for ten to thirty-four years. Sixty-two patients (25 per cent.) showed manifestations of diabetic nephropathy. All had proteinuria as one of the earliest and most constant manifestations. Fifty-five patients had retinopathy, 18 of them retinitis proliferans. Hypertension (a blood pressure of 150/90 or above) was present in 41 patients. Thirty-seven patients were anæmic (Hb less than 12 g per 100 ml.). Vascular calcification was demonstrated by roentgenogram in 47 cases or more than 75 per cent. of the group, and was considered to be moderately or markedly extensive in 37 patients. Thirteen of the 62 patients died during the year of study of renal failure, their average age of death being thirty-three years, and the average age of onset of diabetes being 14.2 years.

Diabetic Retinopathy

It has long been known that diabetics frequently show a retinal lesion which has some similarity to arteriosclerotic retinopathy but has notable differences. The retinal lesions are alike in that the exudates are often small, sharply defined and glistening, and in the absence of papilloedema. They differ in that in diabetes, (a) the lesion is more often bilateral, (b) "waxy" or "soapy" exudates of larger size are not uncommon and (c) round "hæmorrhages" are characteristic (Fig. 12.5), (d) signs of organic arterial disease, though common in diabetic retinopathy, are not an essential component as they are of the arteriosclerotic form. Thanks chiefly to the work of Ballantyne and



FIG 16 5 ($\times 300$) Nodular type of intercapillary glomerulosclerosis showing hyaline masses between capillaries and localized dilatation of the vessels (Dr Norman Ashton)



FIG 16 6 ($\times 250$) Kidney injected with Indian ink to show the close relationship between nodules and aneurysmal dilatation of the glomerular vessels in intercapillary glomerulosclerosis Masson stain (Dr Norman Ashton)

are derived from mucoproteins. In conformity with this, Gilliland and others (1954) have shown by paper electrophoresis and staining with PAS that the protein bound polysaccharide is increased in diabetes, particularly the α_2 and β globulin fractions, and that this increase is greatest in patients with the Kimmelstiel-Wilson syndrome. It is, therefore, not unlikely that the syndrome in which characteristic lesions of the kidney, the retina and the peripheral nerves occur in association with diabetes, is a manifestation of some fundamental metabolic fault. Although generally assumed to be a consequence of diabetes, it would seem more likely to me that diabetes is but one manifestation of the syndrome. Green and others (1950) reported improvement in one case of malignant hypertension in a twenty-eight-year-old diabetic after bilateral adrenalectomy. Luft and Olivecrona (1953) obtained survival in one case out of four in which hypophysectomy was performed for severe diabetic retinopathy. Later (1954), they claim better results. However, it is too early to say to what extent these rather drastic measures have a lasting effect and what light they throw on the basic fault.

The relationship of diabetes and its complications to hypertension remains uncertain. Balme and Cole (1951) found that the blood pressures, measured in 209 diabetics over the age of thirty in the out-patient department, were significantly higher than Wetherby's (1932) values for the population at large. In our series of 500 diabetics attending the diabetic clinic at St. Mary's Hospital, the systolic blood pressure is a little higher and the diastolic pressures a little lower than in our population sample measured under identical conditions, but it is doubtful if the differences are significant. We have, however, not yet completed the analysis or attempted to relate blood pressure to the various manifestations of diabetes. While an occasional patient with the Kimmelstiel-Wilson syndrome has hypertension severe enough to induce the malignant phase, the observations of others have shown that the arterial pressure is often perfectly normal. This correlates well with the underlying vascular lesions. As Ballantyne (1945) originally pointed out and as Ashton (1953) has so beautifully and conclusively demonstrated by injections of the retinal arteries and veins, hypertensive retinopathy and diabetic retinopathy are fundamentally different. In both hypertensive neuro-retinopathy and arteriosclerotic retinopathy the dominant vascular lesions are arterial, the lesions narrowing the arterial lumen. In diabetic retinopathy, by contrast, the dominant lesions are venous, the chief component being the microaneurysm and its complications, the round haemorrhage and the waxy exudate. Arterial lesions do occur in the retina in diabetes, leading to narrowing and complete obstruction of small arterial branches, but they occur late in the disease and are not an essential



FIG 16 5 ($\times 300$) Nodular type of intercapillary glomerulosclerosis showing hyaline masses between capillaries and localized dilatation of the vessels. (Dr Norman Ashton)



FIG 16 6 ($\times 200$)

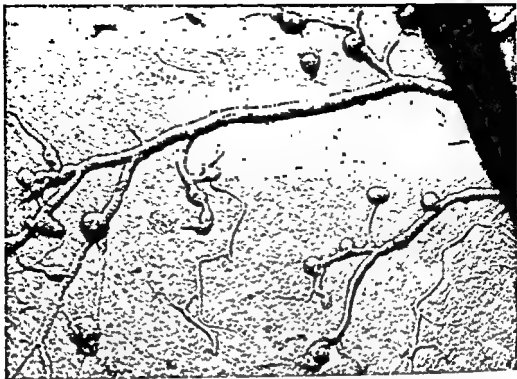


FIG. 16 7 ($\times 150$) Neoprene cast of retinal veins in diabetic retinopathy. Shows extensive micro-aneurysm formation associated with beading of the venules (Dr Norman Ashton)

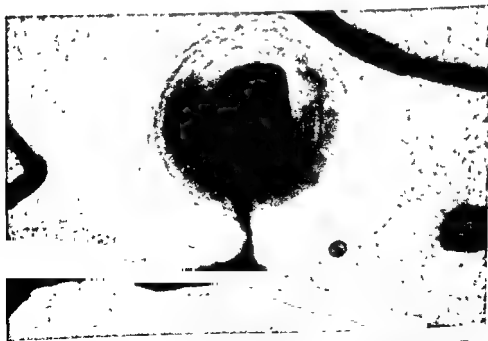


FIG 16 8 ($\times 600$). Micro-aneurysm in diabetic retinopathy. The aneurysm is surrounded with a dense laminated mass of Periodic Acid Schiff positive exudate. Injected with Indian ink. PAS stain (Dr. Norman Ashton)

component of the clinical picture. Venous microaneurysms also occur in other conditions, such as hypertension, but they are seldom, if ever, numerous or large. Thus, the resemblances in the ophthalmoscopic appearances of arteriosclerotic retinopathy (Fig. 12.4), hypertensive neuro-retinopathy (Fig. 12.6) and diabetic retinopathy (Fig. 12.5) are superficial and not basic.

SUMMARY

Nephritis is of two types. In one (Type I of Ellis, Type A of Longcope), the disease is of acute onset, the majority recover, but some go on to a chronic stage characterized by hypertension and renal failure. In the other (Type II of Ellis, Type B of Longcope), the disease is of insidious onset, proteinuria being followed by oedema which is often massive and persistent, progress of the lesion is displayed by hypertension and renal failure. There is some evidence that the mechanism of hypertension differs in the acute and chronic stages of nephritis; but the mechanism has not been identified in either. In both the acute and chronic stages, the characteristic features of the malignant phase may occur.

High blood pressure is not a conspicuous feature of the so-called nephroses, but occurs in some, such as the amyloid kidney, when renal destruction and fibrosis occur.

In diabetes, particularly but not exclusively of long duration, a curious syndrome of a renal lesion, a retinal lesion and a lesion of the peripheral nerves may occur, with or without raised pressure. The retinal lesion has a superficial resemblance to the lesions found in hypertension, but differs in that its basis is a venous rather than an arterial lesion. This symptom complex would seem to result from some basic metabolic fault, not yet identified.

CHAPTER 17

PYELONEPHRITIS

THE part played by chronic pyelonephritis in hypertension is most confusing and most challenging. On the one hand, we have the finding that a high proportion of patients with hypertension in the malignant phase are found at necropsy to show this lesion in their kidneys: 15 to 20 per cent. in Weiss and Parker's (1939) experience at the Boston City Hospital, and 12 out of 35 cases reported by Schottstaedt and Sokolow (1953). I have also found this a not infrequent lesion in patients dying in the malignant phase. On the other hand, Pearman, Thompson and Allen (1940) found that the incidence of hypertension in a series of patients with chronic pyelonephritis was not greater than in patients with goitre without hyperthyroidism, or with gall-bladder disease. This contrast is not entirely explained by the stage of the disease, since it is established beyond doubt that patients with chronic pyelonephritis may run through the whole course to death from renal failure, without ever having a raised arterial pressure. Again the only entirely valid evidence that the kidney is ever responsible for hypertension in man is derived from those cases of hypertension in which disease of one kidney is found, and in which removal of that kidney restores the arterial pressure persistently to a much lower level. Chronic pyelonephritis is the lesion commonly found in such kidneys, often in association with a developmental or acquired abnormality (Pickering and Heptinstall, 1953). Yet there are some cases who show unilateral pyelonephritis and have no hypertension, and others who have unilateral pyelonephritis with hypertension and in whom the pressure is not materially altered by excising the diseased kidney. Chronic pyelonephritis thus seems to offer an unusual opportunity for deciding what, in man, is the nature of the renal fault which can give hypertension. Unfortunately, however, the available evidence, discussed in this and the succeeding chapter, does not enable this decision to be reached. Finally, if it is accepted that chronic pyelonephritis is an infective disease, and this is unproven, and that chronic pyelonephritis can cause hypertension, then it would seem that adequate treatment of the disease by antibiotics at an early stage offers a reasonable chance of eliminating this cause of raised arterial pressure and its consequences.

The importance of pyelonephritis, and particularly its relationship to hypertension, has been brought into prominence relatively recently.

Loehlein (1917) described three cases of pyelonephritic contracted kidney in young women dying of uræmia. He noted that the urine had contained moderate amounts of protein, many leucocytes but very few casts; the heart was hypertrophied in all three cases, and the arterial pressure high in the only cases in which it was measured. He pointed out that insufficient attention had been paid to this type of contracted kidney associated with infection of the urinary passages, and that it was frequently misdiagnosed. Stacmmeler and Dopheide (1930) described five cases, of which four were in young women or girls. Gibson (1928) gave a comprehensive account of pyelonephritis in both its ascending and descending forms, and its acute and chronic phases, based on 109 necropsies of "purulent or semipurulent infections of the kidney." Amongst them were 11 cases of atrophic pyelonephritis, in four of which the heart was hypertrophied, in six normal, and in one less than normal. In the English-speaking world, it was, however, the paper of Longcope and Winkenwerder (1933) which drew attention to the importance of the disease and the reasons why it was so frequently overlooked. They described nine patients, mostly young, and of whom seven were female; five had an elevated and four a normal pressure. They mostly had a long history of rather vague ill-health sometimes of repeated febrile illnesses, and sometimes of urinary infections. Most did not come under observation until they had some symptom referable to advancing renal failure, at which stage the urine was characteristic in its small content of protein, the virtual absence from it of casts, and its large content of leucocytes. *E. coli* was usually grown from the urine. Retrograde pyelograms showed a small and distorted renal pelvis. Weiss and Parker (1939) subsequently made an important and elaborate study.

Despite its frequency¹ and contemporary importance, chronic pyelonephritis has not featured much in the more authoritative works on hypertension. Thus Fishberg (1939) in his admirable and comprehensive work devoted only one page to it. Pyelonephritis may be defined as a focal inflammation of the kidney substance, together with the mucous membranes of the calyces and pelvis of the kidney, usually of the ureters and sometimes of the bladder. The inflammation seems to be a direct response to bacterial invasion.

Now the kidney can excrete bacteria without any invasion of its substance, as in typhoid fever, and certain other bacteræmias. The circumstances that lead to invasion of the kidney are not fully known but include congenital abnormalities, obstruction to the flow of urine, injury to the kidney, instrumentation and perhaps, in a sense which is

¹ Allen (1952), a New York pathologist writes: "The chief causes of contracted glomerulonephritis are . . ."

the chief
a chronic

not clear, lowering of resistance. Since many organisms may invade the kidney, there are many types of pyelonephritis, and it cannot be said that any are yet fully understood. It is usual to omit tuberculous pyelonephritis in an account of the disease. The description of pyelonephritis may be conveniently divided into the acute and chronic phases; in the acute phase, hypertension does not occur; in the chronic phase it may.

ACUTE PYELONEPHRITIS

Acute pyelonephritis is usually classified as descending or hæmatogenous and ascending or obstructive. Acute hæmatogenous pyelonephritis may occur during any acute infective illness, particularly in a pyæmia; and as embolic nephritis in bacterial endocarditis. Acute ascending pyelonephritis or "Surgical kidney" complicates obstructive lesions of the lower urinary passages. Causes of obstruction that may predispose to acute pyelonephritis are: pregnancy, ureteric calculi, strictures and other forms of urethral obstruction, aberrant vessels or neoplasms; metastatic or contiguous invasion of ureters or bladder by carcinoma of the rectum, uterus or adnexæ, hypertrophy or carcinoma of the prostate gland; tumours of the bladder; and finally, spinal cord and brain stem lesions. In both ascending and descending types there are wedge-shaped areas of acute inflammation, the centres of which may contain pus, the bases of the wedges being towards the surface of the kidney and located particularly in the cortex. These areas may suppurate and merge into carbuncle of the kidney (a variety of hæmatogenous pyelonephritis). In the ascending form there are usually intense inflammatory changes in pelvis ureters and bladder, particularly in that part of the urinary tract proximal to the obstruction. In this form the usual organisms are *Escherichia coli*, *Aerobacter aerogenes*, *Streptococcus faecalis*, *Staphylococcus aureus*, and the genera *proteus* and *pseudomonas*.

Clinically, acute pyelonephritis may be divided into two types. In the first or secondary type, the pyelonephritis is a complication of another grave illness, either a generalized infection or a lesion obstructing urine flow. The patient is usually ill, and the onset of pyelonephritis may be diagnosed with difficulty, or the patient may develop fever, pain in the back and loins, with tenderness and rigidity of muscles in the renal angle behind, and the iliac fossa and above it, in front; there may be oliguria or anuria, and the blood urea rises; the polymorphonuclear count is raised. The urine usually contains pus and micro-organisms, but these may be absent if the infection remains closed, that is to say the bacterial invasion is confined to the kidney, and the abscess cavities are closed. Patients with this type of acute pyelonephritis often die.

The second type, or primary pyelonephritis, is generally regarded as not a very serious disease, and has long been known to clinicians as acute "pyelitis."

Acute pyelitis is a disease that may occur at any age and in either sex but is more common in females, particularly as children and during pregnancy. Robertson (1944) has stated that almost every pregnant woman develops ureterectasis and pyelectasis with urinary stasis during the second half of pregnancy and that about 1 to 6 per cent. develop urinary infections. It has for long been assumed that the infection is limited to the mucous membrane of the pelvis, calyces, ureters and bladder. Weiss and Parker (1939), however, drew attention to the fact, previously reported by others, that in this condition the kidney is also involved, the inflammation occurring focally in the interstitial tissue of cortex and medulla to which it is restricted in some, but spreading, in most, to involve glomeruli, tubules and arteries and arterioles. The pelves of the kidney show varying degrees of inflammation, the mucous membrane being red and thickened, and at times showing small ulcers or a pseudo-membrane. As is well known.

In others the fever is associated with pain in the back or of renal distribution, tenderness and rigidity in the renal angle behind and the iliac fossa in front, frequency, dysuria, moderate proteinuria and gross pyuria. In yet others there are few or no constitutional symptoms, or signs, but a complaint of frequency and burning micturition with the usual urinary findings.

Hypertension is not found in acute pyelonephritis.

CHRONIC BILATERAL PYELONEPHRITIS PYELONEPHRITIC CONTRACTED KIDNEY

The chronic phase of bilateral pyelonephritis, to the pyelonephritic contracted kidneys, has been fully described (1933), Longcope (1937) and Weiss and Parker (1939). Following the latter authors it may be described under the following heads: chronic pyelonephritis and healed pyelonephritis.

Chronic Pyelonephritis. In Longcope's series, most of the patients were women between the ages of 16 and 30: in Weiss and Parker's 17 patients, nine were under the age of 40. In adults below efficiency, with or without Longcope's 22 patients, at least five years

it had been present for

from fourteen to seventeen years. "Starting with a pyelitis in childhood, an infection of the urinary tract during pregnancy or, in rare instances, an outspoken acute pyonephritis there may be from time to time attacks of unexplained fever, with or without slight or fairly severe pain in the lumbar regions. These attacks are often accompanied by the passage of cloudy urine. Occasionally there is a history of albuminuria of many years' duration. Often there is a story of malnutrition, or sometimes of retarded growth in children, leading occasionally to rickety deformities. In some instances the progress of the disease is, for years, symptomless" (Longcope, 1937).

In the final stage, the patients present either with symptoms and signs of advanced renal insufficiency, or with hypertension which may be in the malignant phase, or with both. If renal failure predominates, the presenting symptoms are lassitude, loss of weight, nausea and vomiting, breathlessness, or convulsions and coma. If hypertension is the predominant feature, headache, breathlessness, disturbances of vision, or cerebral attacks are the usual complaints. Anaemia, often of a severe grade is usual; oedema is exceptional, unless associated with cardiac failure. Hypertension may be accompanied by signs of enlargement of the heart, neuro-retinopathy and signs of congestive cardiac failure or attacks of left ventricular failure; cerebrovascular accidents and coronary disease are rare.

As Lochlein (1917), Longcope and Winkenwerder (1933) and subsequent authors have stressed, the urine is notable for the slight degree of proteinuria, the numerous leucocytes and the rarity of casts. In the terminal stages there is polyuria with fixation of the specific gravity at about 1.010. *E. coli* can be grown from the urine intermittently.

"One of the most important evidences of the disease is obtained by pyelography. The characteristic change in the pyelogram is a distortion, flattening and reduction in size of the pelves (Fig. 17.1). This may occur without dilatation of the ureters, though in some instances there may be uniform or irregular dilatation of the ureters. An actual enlargement of the pelves of the kidneys is rare. The cystoscopic examination shows, as a rule, no changes in the bladder, though in one case ulceration of the mucosa was observed" (Longcope, 1937).

Weiss and Parker (1939) pointed out, as has been my own experience, that there is no type of kidney disease in which fluctuations of renal function occur so frequently as in chronic pyelonephritis. During the acute episodes in which fever and leucocytosis are common, renal failure may advance even to the stage of coma and uræmic pericarditis, and yet the patient may recover, renal function remaining adequate for years. As a rule, however, renal failure progresses inexorably, though often slowly, to death in uræmia. On post-mortem examination, the

kidneys are usually unequal and reduced in size and coarsely or finely scarred (Fig. 17.2). On section, the pelvis is often relatively dilated and expanded into the calyces; the walls may be thickened and reddened (Fig. 17.3). The renal substance is reduced, especially the cortex, and coarsely scarred. Microscopically, the scarred areas show tubules filled with the so-called colloid casts and lined with atrophic epithelium (Fig. 17.5). The glomeruli show concentric pericapsular fibrosis. The glomerular tufts exhibit a degree of sclerosis varying from slight to complete. The interstitial tissue is increased in amount

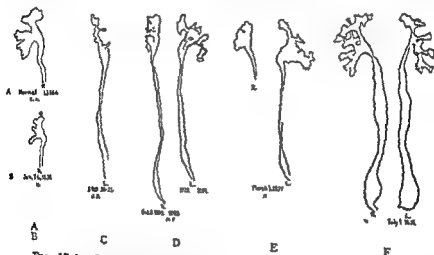


FIG. 17.1 Outlines of renal pelvis and ureters. Note the distortion, flattening, dilatation of ureters (Long).

and infiltrated with lymphocytes and plasma cells (Fig. 17.4), and, in some cases, polymorphonuclear leucocytes. Between the scarred areas the renal substance may be normal. The walls of the pelvis and calyces are thickened and infiltrated with inflammatory cells. In other instances, there is very little normal kidney left. The arteries and arterioles within the kidney usually show intense intimal proliferation or productive endarteritis. Other vascular changes are less common.

Healed Pyelonephritis. Weiss and his colleagues (1934) made this diagnosis in sixteen women from eight to 70 years of age. The patients had a history of difficulty in urinating, of short duration.

of no especial clinical significance. There are, however, a few patients who, after one, or more often more than one, attack of acute pyelonephritis, present with raised arterial pressure, with or without renal impairment. In a smaller group, uræmia without raised arterial pressure ultimately develops. For years some of these patients may have had vague ill-health with moderate anæmia and a dry skin. Renal function tests are usually impaired. The urine may contain an excess of protein or leucocytes; but proteinuria may be negligible and Addis counts may be repeatedly normal. Cultures are sterile. The pyelogram may or may not reveal abnormalities of the pelvis and ureters. In those patients showing elevation of arterial pressure, the hypertension may follow the benign or malignant course.

The clinical diagnosis can usually be established with no more than a fair degree of probability. Otherwise unexplained hypertension or renal failure in a young person should suggest the diagnosis. The condition known as "renal rickets" in children, associated with stunted growth and changes in the long bones, is often due to this lesion. The history of attacks of pyelonephritis and the demonstration of anatomical abnormalities of the urinary tract favour the diagnosis, as does the presence of an excess of leucocytes but no bacteria in the urine. "Toxæmia" of pregnancy occurs relatively frequently.

As described by Weiss and Parker (1939), the post-mortem appearances are very similar to those in the last group, the kidneys being shrunken and showing multiple scarring. They list the following histological changes as characteristic: (1) Presence of so-called colloid casts in the tubules, (2) marked infiltration of the intertubular tissue with lymphocytes and plasma cells, (3) presence of pericapsular fibrosis, (4) inflammation of the pelvis of the kidney, (5) increased connective tissue in the renal capsule with infiltration.

I suspect that this condition, which Longcope does not distinguish from his chronic pyelonephritis, is much more common than we recognize. With some diffidence, for I have not studied the matter in detail, I suggest that the kidneys are not always reduced in size, and that the characteristic lesion is the focal infiltration of the renal tissue with lymphocytes and plasma cells.

UNILATERAL PYELONEPHRITIS

Unilateral pyelonephritis is of especial interest and importance, because of the light it has thrown on the relationship between pyelonephritis and hypertension, and on the extent to which a sustained hypertension in man is reversible when its apparent cause is removed.

A very large number of cases have now been reported in which hypertension has been associated with an abnormality, apparently of one kidney only, and in which that kidney has been excised. Many

different conditions affecting the kidney have been described which will be more fully considered in the next chapter. Here reference will be made to my own experience (Pickering and Heptinstall, 1953). We described 11 cases in which one kidney had been removed for suspected unilateral renal disease in patients with persistent hypertension. One of these was a case of renal tuberculosis: the hypertension was not affected. Four had bilateral pyelonephritis, one kidney being much smaller than the other; the arterial pressure was not reduced in any of these by removing the smaller kidney. Six had apparently unilateral pyelonephritis; in three of them the arterial pressure was unaltered; in three it fell materially after removing the diseased kidney, the falls averaging 85/40, 65/35, and 70/45 mm. Hg maintained for 9½, 10 and 5½ years respectively when our paper was published. In all these three successful cases the arterial pressure remained above the expected norm for their ages, the final pressures being 140/105 in a male aged 43, 140/80 in a female aged 30, and 160/110 in a male aged 39. If we accept provisionally the hypothesis that hypertension was due to the diseased kidney, then we see that removal of the cause failed to affect the hypertension in half our cases.

This is of great theoretical interest because it is in line with what has

been said about the rôle of the kidney in the maintenance of blood pressure.

In a series of nine unilateral cases, the pyelonephritis was entirely *symptomless* in seven, and was only discovered on routine intravenous pyelography in persons presenting with gross hypertension, one had an aberrant renal artery tied for intermittent hydronephrosis, the other presented with hæmaturia. Eight of the nine were under 45 years. In each case the pyelogram showed absent or diminished excretion on one side, with gross reduction in size of the renal shadow and distortion of pelvis and calyces when these were visible. The urine was normal or showed a trace of protein and a slight excess of cells. Fever and leucocytosis were not found. Three of these patients had hypertensive neuro-retinopathy, and in three others the retinal exudates were suggestive of an earlier phase of the same type of retinal lesion; four of these patients had arteriolar necroses in the excised kidney, and may thus be said to have been in the malignant phase of hypertension; only three of our patients were unquestionably in the benign phase.

Thus the clinical recognition of unilateral pyelonephritis depends primarily on intravenous pyelography, which should be done as a routine in all patients under the age of 45 with moderate or gross arterial hypertension, not obviously due to coarctation of the aorta, Cushing's syndrome or nephritis; and in older patients in whom any suggestion of renal pain or a renal infection is found. Absent or diminished excretion on one side, the other side being entirely normal, suggests a unilateral lesion, but must be confirmed by a second intravenous pyelogram, and if necessary by retrograde pyelography. Very occasionally, a normal kidney is not visualized with the intravenous method and may clearly appear when this is repeated; I have saved three such patients from nephrectomy. If unilateral disease seems probable, the ureters should be catheterized, renal function estimated on the two sides, and the urine examined for protein, cells and organisms, before retrograde pyelography is performed. Proteinuria and an excess of white cells (excluding, of course, the effects of traumatic bleeding) with or without a positive culture from the urine on the apparently sound side, suggest bilateral disease, and that nephrectomy is not indicated, since it is unlikely to reduce hypertension and is likely to accelerate renal failure. If the evidence is consistent in suggesting one normal and one abnormal kidney, then nephrectomy is justified and may be expected to reduce arterial pressure in about half the cases. In Rosenheim's (1954) experience, reduction in arterial pressure is more likely in those cases in which the diseased kidney shows good or moderate excretion of dye, than in those in which there is little or no excretion.

Pathological Features of Unilateral Pyelonephritis. In all our unilateral cases, except that of the tuberculous kidney, the excised kidneys showed similar changes to the naked eye and microscopically. They were reduced in size and coarsely scarred; the pelvis was dilated and expanded into the calyces, which were blunted and deformed; the kidney substance was reduced in amount, in extreme cases to a narrow rim of irregular thickness (Fig. 17.3). In the kidney in which an aberrant artery had been tied, the corresponding pole was atrophic. Microscopically, the characteristic feature was the patchy distribution of lymphocytic infiltration in both cortex and medulla, with interstitial fibrosis and destruction of renal tissue (Fig. 17.4). In the larger kidneys the affected areas were separated by normal renal tissue; in the smaller kidneys normal renal tissue was completely absent. The glomeruli in the affected areas showed all grades of change from periglomerular fibrosis to hyalinization and complete disappearance. The tubules were dilated and contained eosinophilic amorphous casts (Fig. 17.5). In the affected areas, the arteries were greatly thickened both in the media and the intima, which showed very conspicuous

intimal proliferation. In the unaffected areas, these changes were not found or were inconspicuous. Arteriolar necroses were found in the excised kidney in both the inflamed and uninfamed areas in four of nine cases of apparently unilateral cases, and one bilateral case.

THE RELATIONSHIP OF HYPERTENSION AND VASCULAR CHANGES TO PYELONEPHRITIS

As we have seen, raised arterial pressure does not occur in acute pyelonephritis, and occurs only sometimes in chronic or healed bilateral pyelonephritis; a substantial proportion of these latter cases run their entire course without hypertension. In those in whom hypertension occurs, its late course may follow the benign or malignant types, described in Chapter 12. The situation is, in a sense, very similar to that discussed in the last chapter, except that the incidence of hypertension in chronic nephritis is probably greater than in chronic pyelonephritis. We may now enquire why some of these patients develop raised arterial pressure and others not, and the relationship of arterial hypertension to organic arterial changes.

Goldring and Chasis (1944) have produced cogent evidence for the view that pyelonephritis does not produce hypertension. Reviewing an extensive literature, they concluded that the incidence of hypertension is no greater in patients with unilateral or bilateral pyelonephritis.

In these cases the operation had been considered successful, but of these Goldring and Chasis rejected 30 because the arterial pressure did not fall to the normal range, or returned to hypertensive levels within six months, or because pre- and post-operative information was too scanty. They considered that an incidence of one in ten of relief of hypertension by nephrectomy is inadequate evidence on which to establish the relationship between unilateral renal disease and hypertension. However, our own experience suggests that about half of the cases of apparently unilateral disease have a large and persistent fall of arterial pressure after nephrectomy, and such seems the general experience in published series of five cases or more (see review by Pickering and Heptinstall, 1953). I do not agree with Goldring and Chasis's conclusion, but their highly critical discussion indicates how uncertain the evidence is.

tension. Longcope wrote "In the four fatal cases in which the blood pressure remained within normal limits or was only slightly elevated . . . the arterioles of the kidney, pancreas, adrenals and intestines appeared normal." "In three cases in which hypertension was marked and was one of the outstanding features of the clinical course a few arterioles were found in the kidney, pancreas, adrenals and intestines which showed moderate hyaline sclerosis, but the lesions were almost minimal in extent." He concluded that the explanation of the hypertension was not clear. Weiss and Parker thought that the hypertension was closely related to the degree of vascular change in the kidneys since they found that : (1) a mild degree of hyperplastic arteriosclerosis in both kidneys is usually associated with normal blood-pressure ; (2) a severe degree of hyperplastic arteriosclerosis in unilateral pyelonephritis may or may not be associated with a hypertension ; and (3) a severe degree of hyperplastic arteriosclerosis in both kidneys is almost always associated with severe hypertension.

In our published series of cases in which a pyelonephritic kidney had been excised surgically for hypertension (Pickering and Heptinstall, 1953), we found gross regenerative intimal thickening (Fig. 11.5) in the small arteries in the affected areas in all cases, while in the normal areas this change was absent. Intimal proliferation of the arteries would thus appear to be a local consequence of the chronic inflammation, and our observations are in accord with the view that this change is in some way responsible for initiating the hypertension, though, of course, they offer no proof. In striking contrast to these proliferative arterial lesions, were the arteriolar necroses, which were found in our cases in the malignant phase, in the unaffected, as well as the affected, areas of the kidney, and in the adrenal glands removed from three patients (Pickering, Wright and Heptinstall, 1952). This distribution is entirely in conformity with the idea presented earlier (Chapters 5, 11 and 13) that these arteriolar necroses are a consequence of the hypertension.

Volhard (1931) and Wilson and Byrom (1941) have put forward the conception of a vicious circle in Bright's disease, the arteriolar necroses of the malignant phase producing renal ischaemia and thus accelerating and perpetuating the hypertension. There is nothing inherently improbable in this hypothesis. Nevertheless, it is not wholly borne out by our experience, since, in one of our successful cases, arteriolar necroses were abundant in the excised kidney and adrenal, while in an unsuccessful case, no arteriolar necroses were found in excised kidney, either adrenal, or a biopsy from the other kidney.

THE TREATMENT OF PYELONEPHRITIS

Treatment of the Infection. Since renal failure and hypertension of the chronic atrophic phase are believed to be the residua of past or



FIG 17.2 The kidneys and ureters from a woman aged 40, who died of malignant hypertension associated with chronic bilateral atrophic pyelonephritis. Note the atrophy, inequality and irregularity of the kidneys and the dilatation and thickening of the renal pelvis.



FIG 17.3 Non-excreting kidney removed surgically from a patient with chronic atrophic pyelonephritis. In this case the other kidney was also diseased. The kidney in unilateral disease is usually of this type. (Scale in cm.) (Pickering and Heptonstall, *Quart J Med.*, 1973, 22, 1.)

(To face p 374)

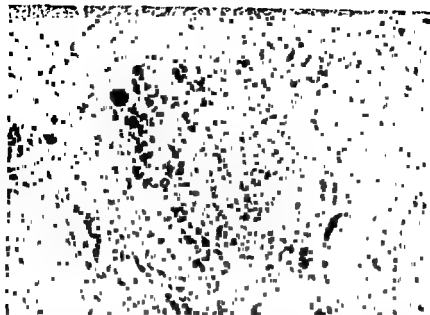


FIG. 17.4 ($\times 96$). Typical pyelonephritic area with disappearance of glomeruli, thickened vessels and lymphocytic infiltration (Pickering and Heptinstall, *Quart. J. Med.*, 1953, 22, 1)

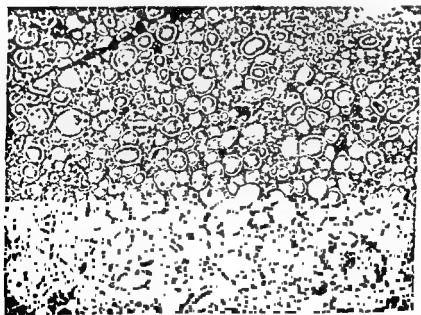


FIG. 17.5 ($\times 66$). Atrophic tubules containing eosinophilic casts in pyelonephritic area. (Pickering and Heptinstall, *Quart. J. Med.*, 1953, 22, 1)

continued infection, their prevention may depend on the recognition and adequate treatment of the acute phase and the chronic active phase. This resolves into two measures; the correction of any obstruction to the flow of urine, and the administration of antibiotics. Of circumstances predisposing to pyelonephritis, the two commonest that are remediable are stone and pregnancy; stones should be removed, and pregnancy may have to be terminated if infection proves obstinate and there are signs of advancing hypertension or renal failure. The antibiotic administered will depend upon the organism and its sensitivity. Stansfeld and Webb (1954) have recently made a strong case for a much longer course of treatment than is usually employed. They have shown that, in infants with pyelonephritis, recovery is commoner and quicker when sulphadimidine is given in full doses for ten days, followed by a long period, two to six months, on a reduced dose. If sulphadimidine is ineffective, chloramphenicol or aureomycin may have to be used, but the case for prolonged treatment is less cogent, since both may have toxic effects which, as in the aplastic anaemia which is reputed to follow the former, may be worse than the disease. My limited experience also suggests that a short course of therapy is useless, and that a prolonged course of antibiotics offers the only hope of arresting the infection.

Treatment of hypertension should be carried out in the same way as outlined in Chapter 16. Since many of these patients are relatively young, sympathectomy is particularly worthy of consideration

STAGNARY

That chronic essential hypertension is a disease of young adults, and by its being the commonest lesion in cases of unilateral renal disease in which excising the kidney abolishes the hypertension. Nevertheless, at an earlier stage in the disease, hypertension is absent, and the disease may run its entire course without hypertension. It is not clear what is the explanation for this, but there is suggestive evidence that hypertension depends on the intimal thickening found in the renal arteries of the diseased kidneys.

CHAPTER 18

MISCELLANEOUS CONDITIONS ASSOCIATED WITH HIGH BLOOD PRESSURE

MISCELLANEOUS AFFECTIONS OF THE KIDNEY

To assess whether pyelonephritis plays any part in the genesis of hypertension, and if so what part, was difficult enough. But in this group of miscellaneous affections, conclusions are even more insecure because of the tendency to report cases of a particular renal lesion that show hypertension without reporting those that do not; because often no account is taken of the distribution of arterial pressures in the general population; and because the possibility is not usually considered that abnormalities of the kidney may be important in the genesis of hypertension, by being the basis for the infective process of pyelonephritis.

SURGICAL AFFECTIONS

Braasch, Walters and Hammer (1940) reviewed the arterial pressures in 1,684 patients subjected to surgical operations on the kidney at the Mayo Clinic and found the incidence of hypertension no higher than in a control group of 975 consecutive cases, taken at random from the registrations at the clinic. Taken as a group, therefore, there is little indication that surgical affections of the kidney play any part in the genesis of hypertension. The incidence of "hypertension" in the various types of surgical kidney is shown in Table 18.1. The highest incidence of hypertension is in atrophic pyelonephritis. They noted that, in contrast to the high incidence of hypertension in atrophic pyelonephritis, the blood pressure was normal in five cases in which operation was performed for congenital hypoplasia. Nephrectomy reduced arterial pressure in seven out of 10 cases of atrophic pyelonephritis—a greater proportion than in any other group. They considered that the incidence of hypertension in association with renal stone was rather greater than Table 18.1 indicates, because there was an unusual number of patients under 50; the incidence of hypertension was notably increased by infection. Blood pressure was returned to normal by operation in 23 per cent. of patients with stone who had had hypertension preoperatively. Hypertension was not frequent in hydronephrosis, was not related to the size of a hydronephrotic sac, and was not usual in bilateral hydronephrosis. The incidence of

TABLE 18.1. *Relative Incidence of Hypertension in Association with Renal Lesions: 1,684 Surgical Cases (Braasch, Walters and Hammer, 1940).*

Diagnosis	All cases	HYPERTENSION			
		Systolic B.P. 145 mm. Hg or more Number Per cent.		Systolic B.P. 180 mm. Hg or more Number Per cent.	
Adenocarcinoma	137	38	27.7	19	13.9
Tuberculosis	158	12	7.6	4	2.5
Pyelonephritis atrophic	43	20	46.5	15	34.9
Pyelonephritis other than atrophic	70	13	18.6	6	8.6
Hydronephrosis	372	51	13.7	21	5.6
Hydronephrosis and stone	577	121	20.9	82	14.2
Stone with infection	164	37	22.5	19	11.6
Stone without infection	52	3	5.7	0	0
Miscellaneous	111	20	18.0	9	8.1

TABLE 18.2. *Relative Incidence of Hypertension in 167 Cases of Unilateral Renal Disease treated by Nephrectomy (Abeshouse, 1941).*

Unilateral renal disease	Total number	HYPERTENSION	
		Systolic B.P. 145 mm. Hg or more	
		Number	Per cent.
Neoplasm	24	3	12.5
Tuberculous	15	3	20
Pyelonephritis, acute	9	1	11
" chronic	9	1	11
Stone, with infection	44	13	30
" without infection	9	1	11
Hydronephrosis, uncomplicated	4	0	—
" complicated	16	3	19
Pyonephrosis	21	3	14
Traumatic	3	0	—
Polycystic	2	1	—
Ectopic	3	0	—
Solitary cyst	2	0	—
Perirenal cyst	2	0	—
Hypoplastic kidney	3	0	—
Horseshoe kidney	1	0	—

hypertension in renal tuberculosis was low. The high incidence in adenocarcinoma was related to age, since more than 60 per cent. were over 50 years.

Crabtree and Chaset (1940) studied 150 consecutive patients in whom nephrectomy had been performed. They give their arterial pressures arranged by age in decades, and point out that their average figures were somewhat lower than those obtained by Wetherby (1932) in his population sample (see page 157). They agree therefore with the conclusion that there is no overall relation between hypertension and diseases of the kidney for which surgery is commonly undertaken. Vascular changes were present in the excised kidney in a high percentage of cases. They noted that elevation of blood pressure was not the rule even in chronic pyelonephritis. Nephrectomy produced no appreciable reduction in blood pressure.

Abeshouse (1941) reviewed the incidence of hypertension (B.P. over 145/90) in 167 consecutive nephrectomies at the Sinai Hospital, Baltimore (Table 18.2). Hypertension was present in 17.3 per cent., a figure slightly lower than that of Braasch, Walters and Hammer. The percentage was highest in renal calculi associated with chronic pyelonephritis. He agreed with these authors in concluding that chronic renal infection accompanied by extensive atrophic changes in the renal parenchyma, and sclerotic changes in the smaller renal vessels ~~in~~ an important factor in the development of hypertension, and that other clinical features of chronic renal infection, severity, duration, impaired renal function, pyuria and pyelographic changes do not appear to exert any appreciable influence upon the development of hypertension.

O'Connor (1942), discussing the results of 219 operations for nephrectomy, stated that in nine a previous hypertension had been improved; these were: calculus disease three patients; hydro-nephrosis three; congenital hypoplasia, two, and tumour of the ureter with hydronephrosis one.

RENAL TUMOURS

Morlock and Horton (1938) studied the arterial pressure in 491 cases of renal tumour, and they compared the incidence of the several arterial pressures arranged by age in the groups: (a) hypernephroma, (b) tumours of other types, which included papillary squamous cell epithelioma, sarcoma, hæmangio-endothelioma, and so forth. The distribution of arterial pressures was practically identical in the two groups and not greatly different from their population averages. No consistent alteration of arterial pressure followed removal of a tumour of either type. Bradley and Pincoffs (1938), on the other hand, report raised arterial pressure in five consecutive cases of adeno-myosarcoma (Wilms' tumour) of the kidney in infants and young children; the

arterial pressure was reduced in two by removal of the tumour, but later rose again as the tumour recurred. Daniel (1939) found systolic pressures below 110 in four, between 110 and 125 in six, and above 125 mm. Hg in eight children, aged eight months to nine years, with Wilms' tumour. Bradley and Pincoffs were unable to extract an active pressor substance from the tumour.

CONGENITAL ABNORMALITIES OF THE KIDNEY

Renal Dwarfism. Ellis and Evans (1933) described 20 cases of the condition known as renal rickets or renal dwarfism, a condition of stunted development associated with bone deformities of the late rickets type, and renal failure. In 17 of these cases, observations on the urinary tract were available; 14 showing varying degrees of dilatation which seemed to be due to obstruction, consequent on a neuro-muscular disorder of the uretero-vesical sphincter. Arterial pressure was greatly raised in two, and above normal in three others; in nine cases there was no hypertension. In the two cases with pronounced hypertension a contracted kidney due to "chronic insidious nephritis" was found. No histological details are given but it is notable that one of these two patients had had "pyelitis" as a child. It seems probable that the lesion to which they refer was chronic pyelonephritis.

Congenital Hypoplasia of a Kidney. Braasch, Walters and Hammer (1940) stated that, in contrast to the high incidence of hypertension in association with chronic atrophic pyelonephritis, the blood pressure was normal in five cases in which operation was performed for congenital hypoplasia. Abeshouse (1941) also found a normal pressure in three such cases. The association of congenital hypoplasia with hypertension was pointed out by Ask-Upmark (1929) who described eight cases, five of them in children.

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"Anlagen." The gross and histological description of the kidneys closely resembles that given in the last chapter for chronic pyelonephritis, and it seems that in his cases this chronic inflammatory lesion was superimposed on a developmental fault, as was the case in the majority of cases of unilateral pyelonephritis described on page 372. A large number of cases has since been described of unilateral hypoplasia of the kidney associated with gross hypertension, often in the malignant phase, in children or young adults. In nearly all these cases

hypertension in renal tuberculosis was low. The high incidence in adenocarcinoma was related to age, since more than 60 per cent. were over 50 years.

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associated with ptosis of the kidney on standing. In each of these patients, the pressure was higher when he or she lay down. Change from the recumbent to the erect posture was accompanied by variable changes in glomerular filtration rate, by conspicuous decrease in renal blood flow and by rise in the filtration fraction. They considered these effects were due to obstruction of arterial flow by kinking of the renal pedicle in the upright position, and subsequent release of renin. Attempts to fix the kidneys were not successful in two cases.

Obstructive lesions of the main renal artery have been reviewed as causes of hypertension by Yuile (1944) who concluded that there had been perhaps too great a tendency to assume the action of the Goldblatt mechanism, merely because of the presence of a lesion which narrowed the lumen of one or both renal arteries.

Freeman and Hartley (1938) describe a 57-year-old man whose left kidney was removed for laceration. The arterial pressure was normal for sixteen months and then rose, the patient dying with malignant hypertension two years after operation. *Post mortem*, an atheromatous plaque was observed partially occluding the renal artery to the remaining kidney, which was extensively involved by pyelonephritis. Hypertension here was ascribed to renal ischaemia, but the long latent period and the clear presence of pyelonephritis at death suggests the latter lesion was important.

Goodman (1952) described a woman of 22 who died in the malignant phase of hypertension. The right kidney weighed 100 g. and was histologically normal, its artery was occluded by recanalized clot 3.5 cm from the aorta. The left kidney weighed 130 g. and showed marked focal scarring and fibrosed glomeruli, atrophic tubules and an overall slight lymphocytic infiltration within the scars. Between the scars the glomeruli and tubules were well preserved. Throughout the section, and especially within the scars, the vessels were greatly thickened with narrowing of the lumen, the thickening being consistent with the "onion skin effect" seen in hyperplastic arteriolar sclerosis. He also attributes hypertension to renal ischaemia, but here again the changes in the other kidney are very reminiscent of chronic pyelonephritis.

Leadbetter and Burkland (1938) reported the case of a boy with hypertension and a small kidney located in the pelvis, its renal artery being almost completely occluded by a smooth muscle plug. Blatt and Page (1939) described a case of lymphosarcoma compressing the renal vessels. I have seen one case of renal artery stenosis in a girl of 15 with one small and one large kidney, the renal artery of the small kidney was almost completely occluded at its mouth. Other examples are quoted by Braun-Menendez and others (1946).

Blackman (1939) stated that arteriosclerotic plaques projecting into

where a full histological description is given, the lesions show the characteristic features of chronic pyelonephritis, namely hyalinization of glomeruli, dilatation of tubules with colloid casts, focal infiltration of the kidney substance with chronic inflammatory cells, and intense intimal proliferation of small renal arteries. Such are shown, for example, by the cases described by Leiter (1938), Clark (1940), de Takats and Scupham (1940) and Killian and Calvin (1941). It would seem extremely probable, therefore, that when hypertension occurs in patients with congenital hypoplasia of one or both kidneys, it is due to the supervention of chronic pyelonephritis.

INJURY AND PERINEPHRITIS

Perinephritis induced in experimental animals by silk, latex and cellophane applied round the kidney causes hypertension. Cases have been described by Sobel (1941) and by Engel (1940) in which injury produced either a perirenal or subcapsular hæmatoma with transient hypertension.

Farrell and Young (1942) described a boy of 18 whose arterial pressure was 154/102 and from whom was excised a right renal hæmatoma enclosing a kidney showing histological changes suggestive of pyelonephritis; ten months later the arterial pressure was 114/74; the hæmatoma was attributed to injury twelve years previously. Braasch and Wood (1942) collected 70 cases with perinephric abscess or perinephritis; 4.3 per cent. had hypertension as compared with 0.1 per cent. of random registrations at the Mayo Clinic.

LESIONS OF THE RENAL ARTERIES

Goldblatt's demonstration that hypertension could be produced by renal artery constriction led to a search for arterial lesions as causes of hypertension. Goldblatt himself (1938b) showed that in some cases of essential hypertension, when the renal arterioles were free of disease, the main renal artery was obstructed.

Ligature of an Aberrant Artery. In two of our cases of unilateral renal disease, ligature of an aberrant renal artery for intermittent hydronephrosis was not followed by hypertension, as shown by examination for life insurance a few weeks and three years after operation (Pickering and Heptinstall, 1953). Both of these subsequently developed hypertension, relieved for over ten years by excising the kidney in one case. Both the excised kidneys showed atrophy of the pole of the kidney whose artery was tied, and chronic pyelonephritis.

Intermittent Obstruction of the Renal Arteries. McCann and Romansky (1940) reported five cases in which hypertension was

on the twelfth day; pressor extracts were obtained by perfusing her kidneys with saline *post mortem*. Fishberg (1942) described five cases in which embolic obstruction of a renal artery was associated with a rise of arterial pressure, which, however, was not observed to last longer than a month. In one of the two cases that survived, the rise in blood pressure only lasted two weeks; in the second case, emboli in one kidney produced no rise of blood pressure, while in the other kidney emboli produced a slight rise maintained during a month's observation.

POLYCYSTIC KIDNEYS

Polycystic kidneys are usually bilateral; unilateral cases have been reported (Rall and Odel, 1949). The bilateral condition is probably an inherited abnormality and occurs at two age periods. In one form, the renal swellings are present at birth and may interfere with it; the children may be stillborn and, if living, commonly die in the first year. In this type the parents are unaffected, but siblings are affected and it is possible that the inheritance is of a recessive character (Fergusson, 1949). In the adult form, the age at death is commonest between 40 and 50, and ranges from 10 to 90; inheritance is probably of the dominant type and up to four affected generations have been recorded.

Opinions as to the incidence of hypertension in polycystic disease have varied greatly. Bell and Clawson (1928), reviewing published cases and their own eight cases of the adult type coming to *post mortem*, concluded that "the available information is therefore strongly against the view that . . .

by persis

whose ar . . . and in 54 of whom (75 per cent.) the systolic arterial pressure exceeded 145 mm Hg. He calculated regressions for blood pressure on age, and age on blood pressure, for his polycystic kidney series and for a control series of . . .

pressure in the polycystic series, but a good correlation in the controls. On the whole, a similar conclusion has been reached by subsequent workers. Holló and Kolbenheyer (1940) give arterial . . .

of their
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impaired renal function. Zemitzsch (1939) gives the incidence of hypertension (not defined) in 180 cases between birth and 85 years;

the renal arteries were found in 86 per cent. and pronounced stenosis in 25 per cent. of 50 cases of essential hypertension. It is difficult to know what importance to attribute to such results; there were no controls, and the characteristics of the circulation through the kidney in essential hypertension are not those of an obstruction to the main artery (see Chapter 7).

Howard, Berthrong, Gould and Yendt (1954) have described six cases with vascular lesions of one kidney in which a severe hypertension was relieved by removing the kidney. Since these lesions may be missed by the common methods of investigation, they may be described in some detail. The first two occurred in men aged 31 and 45, who had had right-sided abdominal pain for which a normal appendix was removed. Hypertension began within a few days or weeks and rapidly became severe. Intravenous pyelography was normal. In the first case, abdominal exploration for a suspected adrenal tumour revealed an abnormal right kidney thought to contain a malignant tumour. The kidney was removed and the blood pressure fell to normal. The kidney contained an infarct in the upper pole. In the second case the right kidney was deliberately explored, contained an infarct and was removed; the blood pressure gradually returned to normal. In two other patients, no opaque medium appeared during intravenous pyelography, and no urine was excreted by the affected kidney during ureteric catheterization, though the renal architecture appeared normal on retrograde pyelography. In both, the renal artery was thought to pulsate less than normally; both showed tubular atrophy. In two further cases, intravenous pyelography was normal, but abdominal aortography demonstrated defects in the renal arteries. In one of these cases shrinkage in size of a kidney, as exhibited by radiograms four months apart, led to the decision to make the aortogram. These cases demonstrate that in a recent severe hypertension, particularly when there is a history of one-sided abdominal pain which might be renal in origin, aortography has to be seriously considered before a renal defect can be dismissed.

It seems relevant to note at this point that Marshall (1951) found in 400 necropsies that the incidence of aberrant renal arteries was significantly higher in those having hypertension during life, or enlarged hearts after death.

Embolism. Hoxie and Coggin (1940) found that the blood pressure had been above 140 systolic and 90 diastolic in 34 per cent. of 205 patients with renal infarction who were examined *post mortem* at Los Angeles County Hospital, but in no instance could it be proved that the rise was due to renal infarction. Prinzmetal, Hiatt and Tragerman (1942) described a woman of 53 with embolism of both renal arteries in whom the arterial pressure rose from 110/95 on admission to 200/120

RADIATION NEPHRITIS

In Chapter 5 the production of renal lesions and hypertension by exposing the kidneys to X-irradiation was described. Similar lesions have been produced in man by therapeutic irradiation of the abdomen, including the kidneys, particularly in seminoma. The standard treatment of this condition is to remove the affected testis, and irradiate the posterior abdominal lymph glands. Luxton (1953) studied 137 men mostly aged 25-50, so treated, and found 27 with proteinuria and 25 with hypertension subsequently, though some patients were not traced. In 13 of these patients, acute irradiation nephritis developed after a latent period of six to twelve months. All showed protein, nine showed casts, and only two, red cells, in the urine. All showed hypertension and cardiac enlargement, 11 had oedema and five serous effusions into pleura and peritoneum. Neuro-retinopathy was found in five patients, of whom three died. Progressive anaemia, not responding to the usual haematinics, was common. Impairment of renal function was usual. Five of the 13 patients died, four within five months of the onset, and one within twelve months. The fatal cases showed a combination of congestive heart failure, left ventricular failure, hypertensive fits, and uraemia. The patients who recovered began to improve about six months after the onset of symptoms. Although proteinuria tended to persist, oedema, hypertension and cardiac enlargement lessened and renal function improved. The treatment used was bed rest and blood transfusion.

In addition to those who had passed from the acute into the chronic stage of radiation nephritis, there were eight patients in whom examination showed proteinuria. In all cases the total X-ray dosage had been 3,000 r. during a period of thirty-five days. Hypertension, proteinuria, anaemia and impaired renal function were the usual findings. Four patients had hypertension conforming to the benign type with moderately raised pressures, and slight proteinuria. Two developed malignant hypertension, symptoms of renal damage beginning eighteen months after irradiation in one case, twenty-four months after in the other. One of these had retinitis and normal renal function when first seen. Both died. Necropsy in four cases showed a fibrous perinephritis; the kidneys were normal in size; almost all glomeruli were abnormal, the consistent change being hyaline obliteration of capillary loops; intertubular fibrosis was widespread and the tubules were mainly atrophic, fibrinoid necrotic lesions of arterioles were present in varying amount. Chest radiographs showed that the heart began to enlarge about eight months after the start of radiotherapy, although blood pressures were not obtained at that time in these patients.

139 had hypertension and renal insufficiency ; 10 renal insufficiency without hypertension ; four, all over 60, hypertension without renal insufficiency ; and 27 neither hypertension nor renal insufficiency. He therefore concluded that, except in the older age groups where essential hypertension cannot be excluded, hypertension is frequent in polycystic kidney, and is dependent on renal insufficiency.

The kidneys in polycystic disease are enormously enlarged, up to 650 g. for a unilateral cystic kidney, 3,500 g. for a pair of affected kidneys (Allen, 1952). The capsular surface is raised by cysts varying from microscopic size to several centimetres in diameter. On cut section the outstanding feature is the presence of cysts, of various sizes, filled with pale watery or bloodstained fluid, between which there are remnants of renal substance. Pyelonephritis and glomerulonephritis may occur in this tissue (Allen, 1952). Schacht (1931) examined the arteries and arterioles and found them thickened in polycystic kidneys but gives no details ; he also found a high incidence of retinal vascular sclerosis, and concluded the arterial disease was generalized. Ritter and Bachr (1929), injecting radio-opaque material into the renal vessels, found them extensively narrowed as a result of sclerosis and suggested that this narrowing led to atrophy of the parenchyma and further hypertension.

Lambert (1947) has shown that in the newborn the cysts are closed cavities arising from nephrons isolated from the pelvis ; in the adult the cysts may develop from the glomeruli or from the tubules.

The newborn infant who dies of polycystic disease usually does so from uræmia. It is doubtful whether in the adult form any abnormality can be detected during infancy and early childhood, even by pyelography (Fergusson, 1949). The patient with the adult form may present at any age from the teens to old age with the following complaints : hæmaturia, pain in the back or loins, symptoms of a urinary infection, abdominal tumours, the complications of hypertension or of renal failure. The tumours are usually easily palpable on careful abdominal examination ; the urine may contain protein, cells and casts, and the pyelogram is characteristic, showing elongation of the pelvis and calyces with curved indentations caused by individual cysts. The course is usually long, punctuated by bouts of hæmaturia, pain and urinary infection, and the end stage is usually dominated by renal failure, though it may be by the consequences of hypertension. There is probably no condition in which such an advanced degree of renal failure can remain stable for so long. When hypertension occurs, it is rarely severe and is nearly always in the benign phase. Zemitzsch (1939) stated that the malignant phase did not occur. I have seen one case in the malignant phase, the pathology of which was described by Heptinstall (1953).

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OTHER MISCELLANEOUS CONDITIONS

Beri-Beri. Walters (1953) described an outbreak of acute cardiovascular beri-beri amongst pearl divers in the Persian Gulf, three months after their fleet had put to sea. The features of the outbreak were gross anasarca, cardiac enlargement and failure, arterial hypertension, and poverty of signs of peripheral neuritis. Administration of aneurin improved the condition, but usually increased the arterial pressure during the first few days it was administered, so that those who had normal pressure on admission showed pressures above 150/90 during that time. The single patient (of 12) who showed no hypertension died within twenty-four hours of coming under treatment. Raised arterial pressure in beri-beri, especially during the initial phases of the response to aneurin, has also been described by others to whom Walters gives reference.

After Injury. Grant and Reeve (1951) found that some patients show elevated pressures (over 140 systolic) for a short time after wounding, the pressure returning to normal with rest, warmth and morphine. This usually occurred after small or moderate wounds, and with blood volumes within 20 per cent. of the predicted normal. They attributed the raised pressure to the emotional and sensory stimuli associated with injury.

Lead Poisoning. In the nineteenth century, when lead poisoning was common, this intoxication, together with gout, syphilis and alcohol, was regarded as an important aetiological factor in producing granular contracted kidney and arteriosclerosis. It was observed that the blood pressure commonly rose during the attacks of colic. Saturnine encephalopathy, or lead convulsions, were often associated with loss of vision, with atrophy or swelling of the optic disc and sometimes with neuro-retinopathy. In some of these patients the arterial pressure was very high and Labadie-Lagrave and Laubry (1906) described a patient in whom vision was almost completely lost when the arterial pressure rose above 250 mm. Hg, returning when amyl nitrite had reduced the arterial pressure to 170 mm. Hg. Vision was again lost an hour later, to return the following day when the arterial pressure gradually fell to normal. Elschnig (1898) described a painter in whom the retinal arteries became obliterated when vision was lost during an attack of lead colic. There were some therefore who saw arterial spasm induced by lead intoxication, as the central feature in the clinical picture of this condition.

With improvement in industrial conditions, water supply, and the like, lead poisoning has become much less common, and more recent observations provide alternative explanations for at least some of the phenomena and leave some doubt as to whether, in general, there is much rise of arterial pressure, at least in chronic lead poisoning. The

evidence is reviewed by Hamilton (1934), who gives full references. Briefly, there is now a good deal of evidence that the encephalopathy is largely due to a lead meningitis. There is no really satisfactory evidence that arteriosclerosis, renal disease and hypertension are commoner in those who suffer from lead intoxication than in the population at large. On the other hand, the statistics of the Metropolitan Life Insurance Company show a higher proportion of deaths from cardiovascular renal disease in painters, plumbers, and printers than in men of the industrial class in general. In a brief and imperfectly documented account of 340 cases of chronic lead poisoning, Greensfield and Gray (1950) describe the arterial pressure of the entire group as essentially normal, though hypertension was observed for two to three weeks, in three out of 40 patients with acute lead poisoning.

The results of poisoning experimental animals with lead are also contradictory. Domínguez (1928) did not, while Beckmann (1925) did, observe hypertension develop in rabbits. Griffith and Lindauer (1944) observed a progressive rise in blood pressure in rats given lead acetate. Perhaps the best experiments are those of Fouts and Page (1942) who gave enough lead to produce bloody diarrhoea and a lead line, on four occasions in thirty-four months in one dog, without observing any rise of pressure, proteinuria or anaemia. One kidney was removed and the lead resumed. The dog rapidly lost weight, and after twenty-seven days developed lead poisoning with "encephalitis," but no hypertension or proteinuria. It received a total of 32.59 g. lead over three years. Another dog died of lead poisoning after receiving 1.99 g. lead and likewise exhibited no rise of blood pressure.

SUMMARY

Hypertension may occur in a variety of congenital and acquired lesions of the kidney, and it may follow the usual pattern of the benign and malignant courses. There is suggestive evidence that in some of these conditions, but not in all, the onset of hypertension may be due not so much to the renal disease as to the associated lesions. In pyelonephritis without aortic lesions, excising the kidney abolishes hypertension. Nothing else is known about the mechanism of the hypertension.

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CHAPTER 19

POLYARTERITIS NODOSA

POLYARTERITIS (periarteritis) nodosa is relevant to our subject for two reasons. From the theoretical standpoint, it is important because its basic lesion, in which fibrinoid necrosis of the arterial wall is a prominent component, has many points of resemblance to that of the malignant phase of hypertension, though its pathogenesis is totally different. From the practical standpoint, polyarteritis nodosa may present with a clinical picture resembling acute nephritis or malignant hypertension, though with certain added features that enable a diagnosis to be made. The disease was first described by Kussmaul and Maier in 1866. Good reviews of the previous literature may be found in the articles by Grant (1940) and Davson, Ball and Platt (1948). This account owes much to Dr. G. A. Rose who, working in my Department, for the Medical Research Council, has analysed 111 case records collected from several hospitals in England and Scotland.

Polyarteritis nodosa is an inflammatory and necrotizing lesion of the small and medium sized arteries. Its manifestations are local and general. Its local effects are largely attributable to the local inflammation, to hæmorrhage, and to arterial obstruction. The general effects are similar to those of many infections.

The anatomy of the lesion has been well described by Gruber (1926), Grant (1940) and Davson, Ball and Platt (1948). The name is derived from the whitish nodular thickenings that may be visible along the course of arteries, particularly in mesentery, heart, kidneys, pancreas, liver, spleen, gut, muscle, peripheral nerves and skin; less frequently in lungs and central nervous system. More frequently, nodules are not seen and the macroscopic changes in the organs are of focal inflammation, bacterial infection, or hæmorrhage and the nature of the lesion is only revealed on histological examination. The lesions vary greatly in size, severity and distribution, and it is this variation that determines the great variety of clinical pictures.

Before about 1940, most of the cases that were diagnosed presented *post-mortem* nodular arterial lesions that could be seen macroscopically. Since then, the proportion of cases in which no such lesions are seen on mesenteric, coronary and similar sized arteries has increased. The total incidence of the disease also seems to have increased. There is a suspicion, therefore, that there may be more than one type of the disease, and that that affecting the smaller vessels may be related to



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[illegible]

the frequent use of sulphonamides and penicillin. This suspicion is, however, not fully borne out by the evidence.

On microscopic examination, the characteristic lesions are found in medium sized and small arterioles, and consist of a fibrinoid necrosis of the arterial wall together with a surrounding inflammatory reaction. The necrotic portion of the vessel, as in malignant hypertension, stains a bright pink and appears slightly granular in sections of tissue fixed in formalin and stained with hæmatoxylin and eosin. The necrosis affects mainly the inner part of the media and subintimal regions, but the whole thickness of the wall may be involved. The fibrinoid may break through the elastic lamina, encroach on the lumen of the vessel and, or, enter the adventitia. Aneurysms may form, and are the basis of some of the macroscopic nodes. The majority of nodes are due to inflammatory thickening in and around the artery, usually, the lumen in the centre of a node is narrowed. Hæmorrhage may occur into the surrounding tissue. Thrombi often form within the vessel. Only short stretches of vessel are attacked, particularly at points of branching. The type and degree of the inflammatory cellular reaction varies greatly; at one end of the scale the tissue is so densely infiltrated with polymorphonuclear leucocytes that the picture resembles a purulent inflammation; at the other, there is little sign of a tissue reaction. Fig. 19.1 shows a fairly characteristic acute lesion. In most cases some of the lesions show signs of healing in the form of granulation or scar tissue. As a result, the vessel becomes thickened, locally or generally, with interruption of the internal elastic lamina, fibrosis of the media and adventitia and small arteries and arterioles may

Davson,
kidney. Tw

... type, the clinical presentation was of acute nephritis with additional features. The kidneys were enlarged and pale, and showed widespread patchy fibrinoid necrosis of glomerular tufts with peri-glomerular inflammatory cell infiltration (Fig. 19.2), epithelial crescent formation and partial fibrosis of the tufts. Tubules might be dilated or atrophied. Typical polyarteritic lesions were found in other organs. In the second type, hypertension, often in the malignant phase, dominated the clinical picture and polyarteritis of the renal arteries was found in four of the five cases. They noted the resemblance between the lesions found in polyarteritis, and those in malignant hypertension and give these points of difference. In malignant nephrosclerosis, arteriolar necrosis is practically confined to afferent arterioles and is not associated with perivascular round cell infiltration; endarteritis fibrosa is a diffuse lesion of the intralobular arteries; the larger renal arteries, such as the arcuate, show varying degrees of elastosis; and in the arcuate and



FIG. 191 (x 140) Polyarteritis nodosa affecting arcuate artery of kidney. Note area of fibrinoid necrosis of arterial wall, and surrounding cellular inflammatory reaction. This inflammatory reaction is one of the features distinguishing this lesion from that of malignant hypertension (Dr H. Spencer.)

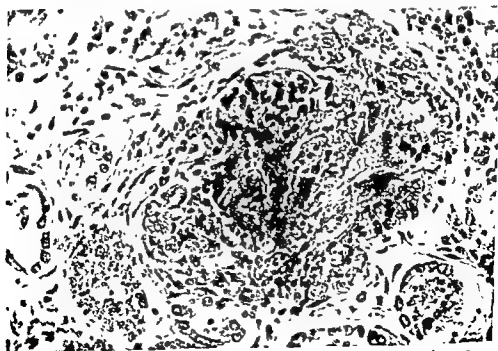


FIG.

most cases, arterial pressure is normal in the early stages of the disease. When hypertension does occur in polyarteritis, it seems to be the consequence of healed polyarteritis of the renal arteries. The hypertension of polyarteritis not infrequently becomes severe enough to enter the malignant phase, when the true lesions of malignant hypertension are added to those of polyarteritis.

CLINICAL FEATURES OF POLYARTERITIS NODOSA

As has been recognized since the original description by Kussmaul and Maier (1866), the clinical manifestations of polyarteritis nodosa are made up of two components: those of a generalized disease, and the local consequences of the vascular lesions. Since these local consequences are so numerous and varied, cases may present in many different ways. Moreover, the chief features exhibited by an individual patient may show very considerable changes, as one phase of the illness succeeds another. Polyarteritis is commoner in males than females. It can affect any age but is commonest *post mortem* in the elderly and most commonly diagnosed clinically in young adults.

General Effects The general characteristics are those which we associate particularly with chronic infections, fever, loss of weight, weakness, tachycardia, anæmia, leucocytosis and high erythrocyte sedimentation rate (E.S.R.). These general features may come and go as the disease relapses and remits, but some, or most, are seldom absent at some stage, and the E.S.R. tends to remain high even when the other features are absent.

Local Effects The most characteristic local lesions are nodules, and consist of nodules from a papule to a necrotic ulcer. Necrosis, ulceration and hæmorrhage into the nodule are all common. In healing, such lesions tend to leave a purple reticulation.

The most characteristic local lesion is that of the peripheral nerves, producing sensory and motor loss in the distribution of the affected nerve, and thus an asymmetrical polyneuritis; more rarely, the polyneuritis is symmetrical. Most of the vascular lesions of the central nervous system in polyneuritis seem to be related rather to the hypertension, which is sometimes present. Nevertheless, such lesions are not infrequently found in the absence of hypertension.

cor
joint as in rheumatic fever, or it may be chronic, resembling rheumatoid arthritis

The limb arteries very rarely show nodules that can be felt; I have

large arteries, rupture or loss of the internal elastic lamella is never seen, nor was recanalization of thrombus seen in the vessels. In *polyarteritis nodosa*, the vascular necrosis is constantly accompanied by perivascular inflammatory cell reaction, and, commonly, medium sized vessels are involved as well as arterioles. The healed phase of *polyarteritis* is recognized by focal rupture or loss of the internal elastic lamella, by fibrosis of the media and perivascular tissues, in which iron pigment may be found, and by severe intimal fibrosis in which capillaries may be present, indicating that organization of thrombus has occurred.

Temporal arteritis (Hutchinson, 1890; Horton, Magath and Brown, 1934; Cooke, Cloake, Govan and Colbeck, 1946), or giant cell arteritis is another condition which has to be distinguished from *polyarteritis*. This condition, restricted to the elderly and commonest in males, affects usually larger arteries, particularly the main branches of the aorta and superficial vessels, especially the temporal and retinal arteries. The dominant feature is the infiltration of the media and other coats of the vessels with a variety of inflammatory cells in which giant cells are not uncommon, particularly in association with the fragmented internal elastic lamina and in which polymorphonuclear leucocytes are rare. Fibrinoid change is less conspicuous than in *polyarteritis nodosa* (Heptinstall, Porter and Barkley, 1954).

Zeck, Smith and Weeter (1948) and Knowles and others (1953) distinguish from *polyarteritis* a condition which they term hypersensitivity angiitis, affecting the small arteries of viscera, affecting also veins, and characterized by fibrinoid necrosis of the arterial wall, with a pleomorphic exudation within and around the vessels. Many clinicians suspect that the apparent increase in the incidence of *polyarteritis* is due chiefly to a type affecting small vessels. My colleagues who have studied the problem tell me that, in their experience, a distinction cannot be made between this condition and *polyarteritis nodosa*.

lesions closely resembling those found in human *polyarteritis* were found. What they were presumably dealing with was the arterial lesion of the malignant phase of hypertension (see Chapter 5). In the rat with experimental hypertension, as Wilson and Byrom (1939) described and Grant (1940) confirmed, fibrinoid necrosis may produce aneurysmal dilatation and be accompanied by a cellular infiltration that closely resembles *polyarteritis nodosa*. In the rabbit the fibrinoid necrosis of severe experimental hypertension has no such resemblance. In man there is no doubt whatsoever that raised arterial pressure is not concerned in the pathogenesis of *polyarteritis nodosa*, since, in

pressure is normal at this stage. In fact, what appears to be a slightly atypical nephritis with rapid renal failure and normal blood pressure should excite suspicion of polyarteritis. Should the patient survive this acute phase, he tends to develop progressive renal failure and hypertension and behaves, in fact, very much like a case of chronic nephritis.

Patients presenting with Hypertension. Of Davson, Ball and Platt's five cases of renal polyarteritis, the clinical picture was dominated by severe hypertension in three; two of these appear to have had hypertensive neuro-retinopathy, and thus to have been in the malignant phase. All had proteinuria and three of the five died in uræmia. All had other symptoms, abdominal, thoracic, rheumatic, or neuritic, compatible with polyarteritis nodosa.

Davson, Ball and Platt reviewed their own cases and those previously reported, and leave the impression that there is no close relationship between renal polyarteritis and hypertension. Rose, however, has come to a different conclusion and I thank him for allowing me to quote here a summary of the relevant section of his results.

"Valid records of arterial blood pressure were available in 55 cases. In 24 cases the pressure was normal on all occasions; at necropsy in these cases recent arterial and glomerular lesions were common, whereas healed lesions with associated ischemic changes were seen only once. In 15 cases hypertension was observed to develop during the course of the disease; urinary evidence of renal lesions preceded any rise in pressure in all cases where data were adequate. At necropsy 12 of them had either healed renal polyarteritis or chronic glomerulitis; the other three had ischemic changes in the kidneys not attributable to arteriosclerosis, but without positive evidence of polyarteritis. In 16 cases the blood pressure was raised at the initial measurement; but in 14 of these, this measurement was made several months after the onset of the disease, and only in the other two cases was there definite evidence that hypertension preceded polyarteritis nodosa. Furthermore, in eight cases in this group, the hypertension was found to be advancing rapidly during the period of observation, and at necropsy all but two of the 16 cases had healed renal polyarteritis. It is concluded that hypertension in polyarteritis nodosa is in almost all cases a sequel of renal polyarteritis or glomerulitis, but that the pressure only rises during the healing or healed stages of these lesions. Once initiated, hypertension is progressive; it terminated in the malignant phase in at least 11 patients in this series (10 males and one female). At necropsy the severity and extent of polyarteritic lesions were approximately the same in cases with normal and cases with high pressures, healed lesions were more frequent in the latter."

not yet seen such a case. Occlusion of limb arteries may produce intermittent claudication, gangrene or Raynaud's phenomenon; disappearance of the radial, posterior tibial or dorsalis pedis pulse on one side may be an important corroborative finding.

The signs of cardiac involvement are chiefly those of cardiac failure and enlargement. The clinical picture of myocardial infarction is surprisingly uncommon, though small infarcts are common *post mortem*.

Involvement of the alimentary canal may produce abdominal pain, usually rather ill-defined and unlike that of peptic ulcer but sometimes indistinguishable from it; physical signs are usually scanty. Haematemesis and melæna also occur.

Involvement of the lungs tends to produce a type of disease with characteristics of its own. Clinically, the patient may present with typical bronchial asthma, accompanied by a high eosinophilia. Or there might be a pneumonic illness, or cough and sputum, termed bronchitis, with radiological changes ranging from a small area of consolidation to a wide dissemination of destructive lung lesions. Necropsy reveals nodular or caseous lesions resembling pulmonary tuberculosis, except for the total absence of tubercle bacilli. Rose and Spencer (unpublished observations) think that the histological lesion in such cases presents some points of difference from those of classical polyarteritis. Thus it tends to be more granulomatous and to contain giant cells and many eosinophils; granulomatous lesions may also be present in organs not obviously related to arteries. Because of their histological changes and because of the tendency to a high blood eosinophilia (exceeding 1,500 per mm.³ at some stage in 50 per cent. of cases), they propose the name eosinophilic polyarteritis for this group.

INVOLVEMENT OF THE KIDNEY AND ITS RELATIONSHIP TO HYPERTENSION

As has been noted, Davson, Ball and Platt (1948) observed two types of lesion of the kidney, a widespread necrosis of glomerular tufts and polyarteritis of the renal arteries. Patients belonging to the first group tend to present as atypical acute nephritis, the second as cases of hypertension, often in the malignant phase. These observations have been confirmed by Rose.

Cases presenting like Nephritis. The disease usually begins with a generalized illness with fever and leucocytosis; muscle pains, chest symptoms and abdominal pain are common. Proteinuria is invariable and a macroscopic, or heavy microscopic, hæmaturia with red-cell casts. The urine is often scanty and rapid renal failure is common. As

TREATMENT OF POLYARTERITIS NODOSA

The cause of polyarteritis is still unknown. Although there is some evidence to suggest an allergic origin, this is quite unproved. So far, nothing is known to affect the course of the disease, with the possible exception of ACTH and cortisone. There would seem little doubt that cortisone in adequate doses will suppress the acute manifestations of the disease, and there is some evidence that it prolongs life. It should be begun in doses of 200 mg. daily, and the dosage adjusted to the least that will completely suppress symptoms or, if this is large, that producing some alleviation without intolerable side effects. The dose should be adjusted to the relapses and remissions.

If hypertension has not developed, then there is the possibility that, by preventing renal polyarteritis, the blood pressure may remain normal. However, healing of such renal lesions as exist may produce hypertension, even though further lesions may be prevented. If hypertension already exists, then great care should be exercised with cortisone which, through its actions in retaining salt and water and raising arterial pressure, may precipitate a fatal cardiac failure. In patients with hypertension, therefore, it is imperative to bring this under control with methonium or other drugs, before, or at the same time as, cortisone is given. It is just as necessary to continue to control the hypertension throughout the patient's life, for clinical observation has clearly established how prone is the hypertension of polyarteritis nodosa to enter the malignant phase.

OTHER COLLAGEN DISEASES

Disseminated Lupus Erythematosus. Disseminated lupus erythematosus, like polyarteritis nodosa, produces a very varied clinical picture. This may include a rash, affecting particularly the cheeks, nose and extremities, arthritis, pleurisy, pericarditis.

Arteries are more commonly affected than veins, and high blood pressure is not infrequent.

Fibrinoid necrosis of arteries and of connective tissue collagen is a striking feature at necropsy (Klemperer and others, 1941). In most of the cases, the arterial pressure is not raised. The retinopathy and the fibrinoid arteriolar necroses are not due to raised arterial pressure, and are presumably part of the widespread connective tissue disturbance, which also finds expression in the fibrinoid necrosis of skin collagen. Nevertheless, it is possible that there may be a tendency to high blood

DIAGNOSIS OF POLYARTERITIS NODOSA

Polyarteritis nodosa may present in a variety of ways. Some of the more striking clinical syndromes are these :—

(1) As a many system disease with symptoms explicable on a vascular basis.

(2) As acute nephritis with a normal blood pressure and the symptoms and signs of a constitutional disease.

(3) As rapidly advancing hypertension associated with an otherwise unexplained constitutional disease.

(4) As an asymmetrical polyneuritis.

(5) As asthma with a high eosinophilia ; pulmonary consolidation or excavation and involvement of other systems.

(6) Resembling subacute bacterial endocarditis, with fever, urinary abnormalities, and cardiac enlargement, a systolic murmur, and sometimes cardiac failure.

(7) As rheumatoid arthritis developing lesions in other systems.

In some cases of polyarteritis nodosa, the clinical features of the disease are so striking as to leave little doubt of the diagnosis. In the majority, however, they are less conclusive and a wide variety of diseases, the reticuloses, subacute bacterial endocarditis, and malignant disease are possible alternatives. In such cases, no time should be lost before trying to confirm the diagnosis by biopsy. If there is a nodule or skin lesion, this should be excised. In the case of the skin, an early lesion should be chosen ; when ulceration or necrosis have occurred it is difficult to decide whether arterial changes are primary or secondary. If such a lesion is lacking, then a piece of muscle (about 3 ml.) should be excised, choosing, if possible, one that is painful or tender. In any case, the block should be examined in serial section before a negative diagnosis is returned. In cases which I suspect seriously of the disease and in which a first biopsy is negative, I take two more as soon as possible.

Disseminated lupus erythematosus is not unlike polyarteritis pathologically, in that fibrinoid necrosis is also found in vessels, but those affected are predominantly arterioles. There is little or no inflammatory reaction, "wire loop" lesions occur in the glomeruli, and the "onion skin" lesions in the spleen. Clinically, disseminated lupus also produces a variegated clinical picture in which fever, wasting and weakness are common findings. But in disseminated lupus, females are much more commonly affected than males ; serositis is common, retinal exudates are sometimes found in the absence of hypertension, the distinctive rash may be present ; hypertension is infrequent, though proteinuria is common ; the characteristic L.E. cells are found in the blood and leucopenia is the rule.

CHAPTER 20

CHROMAFFIN CELL TUMOUR (PHŒOCHROMOCYTOMA)

CHROMAFFIN cell tumour, otherwise known as paraganglioma or phœochromocytoma, provides one of the most exciting problems in the field of hypertension. Here is a tumour of secretory tissue which contains abnormal quantities of the sympathetic nervous transmitters, which secretes abnormal amounts of these substances into the blood continuously and in paroxysms, which produces the most dramatic, disabling, and dangerous attacks often misdiagnosed in the past; a tumour moreover which can be removed surgically, providing a more or less complete cure. The clinical scientist finds here one of nature's

leads to a triumphant dénouement. Not unnaturally, therefore, these rare tumours have gained a share of medical literature disproportionate to their numbers. They have been collected and analysed from time to time. This account is particularly indebted to the papers by Rabin (1929), Howard and Barker (1937) and Mackeith (1944).

The chromaffin cell tumour or phœochromocytoma most frequently, but by no means always, arises in the adrenal. Its essential constituent is a polyhedral cell larger than that found in normal suprarenal medulla, and having an abundant finely granular cytoplasm. These cells are arranged in nests or cords separated by a thin connective tissue stroma rich in blood vessels. The cells take a brown stain with chrome salts, hence their name. The tumours can arise from any part of the sympathetic nervous system but nearly all those displaying the symptom complex described here, have been found to arise in the abdominal cavity. Paragangliomata have been described arising from the carotid body, the thoracic sympathetic chain, the sacrococcygeal body and the wall of the intestine, but few of these are true tumours of chromaffin tissue (see Rabin and Mackeith for references). In Geschickter's large group of carotid body tumours there was nothing suggestive of paroxysmal hypertension in any of the clinical records (Howard and Barker, 1937). Mackeith collected 165 chromaffin cell tumours.

majority of these extra-adrenal tumours were retroperitoneal between

pressure in those with extensive renal involvement. Bywaters and Bauer (personal communication), found a marked rise of pressure in 30 of their 58 cases. Jessar and others (1953) found hypertension in 18 per cent. of 44 cases. Tumulty (1954) found that 15 of 105 patients with disseminated lupus had arterial pressures over 140/90 ; in all but one, hypertension " did not develop until there was a very pronounced degree of renal impairment, including nitrogen retention."

Dermatomyositis or Scleroderma. Raised arterial pressure is not common in this condition. One case which I saw from the onset of her illness died with a terminal malignant hypertension (Lewis, 1940).

SUMMARY

The anatomical basis of polyarteritis is fibrinoid necrosis of the arterial wall associated with an inflammatory reaction. The lesion is not caused by raised arterial pressure and its pathogenesis is unknown. The disease produces a varied clinical picture, two types of which resemble other diseases considered in this book. Extensive involvement of the glomeruli produces a clinical picture resembling acute nephritis, in which hæmaturia, oliguria and rapid renal failure occur, but usually without hypertension. Healing of lesions affecting the arteries of the kidney produces hypertension which tends to be rapidly progressive and to end in the malignant phase.

■ reddish-purple mottling round the mouth; the body was pale and there was a cold perspiration. The neck veins were engorged, the pulse quickened and the arterial pressure frequently exceeded 300/180 mm. Hg. The heart enlarged during the attacks, and there was frothy sputum, and other signs of pulmonary oedema. The fundi were normal but the nail-folds showed entire obliteration of the capillaries when the blood pressure reached 170 mm. Hg, and reappearance only when the blood pressure fell below that level. Operation was performed because of the idea that the abdominal sympathetic nerves might be involved, and a tumour, 6 × 4 cm. lying behind the tail of the pancreas, and impinging against the upper pole of the left kidney, was removed. This was considered at the time to be a retroperitoneal malignant blastoma, but subsequent examination showed it to be a chromaffin cell tumour. After operation the attacks ceased and the systolic blood pressure was 120 mm. Hg.

CLINICAL FEATURES

Patients with chromaffin cell tumours may present in four ways (1) with the characteristic attacks described in the two patients above; (2) with persistent hypertension in the benign or malignant phase; (3) very rarely with Addison's disease due to pressure of the tumours on the adrenal cortex; (4) with no symptoms. Only the first two will be considered here.

(a) *Patients presenting with Paroxysms of Hypertension*

This is the form that is most frequently diagnosed. Sometimes the attacks extend over many years; they may steadily increase in frequency or severity; or they may remit and relapse. In many cases of short duration the arterial pressure is normal between attacks; and this may be so even when attacks have extended over many years (Hamilton and others, 1953). In 11 of the 18 cases analysed by Howard and Barker (1937) there was persistent hypertension and in four of them, who were followed for moderately long periods of time, the blood pressure between attacks rose from "normal levels to persistent hypertension, though of course rising still further with the paroxysmal episodes."

The paroxysms are, we now know, produced by the sudden release into the circulation of relatively large amounts of mixtures of noradrenaline and adrenaline, the former tending to predominate. These attacks very commonly come on without any ascertainable precipitating cause, but almost every kind of event has been incriminated, the commonest being movement. The symptoms (Table 20.1) in the attack vary greatly from one case to another, but by far the commonest

the kidneys, but one (Leriche, 1934) was the size of a cherry and lying between the aorta and vertebral column. It was not found at the first operation on the right side. Most of these extra-adrenal chromaffin cell tumours arise in the organs of Zuckerkandl, paraganglia situated along the aorta near the origin of the inferior mesenteric artery (e.g. Fullerton and others, 1954). In the foetus these organs contain appreciable amounts of noradrenaline (West and others, 1953).

The right adrenal is much more commonly involved than the left (ten to three in Howard and Barker's series). Of Mackeith's 152 cases, 16 had bilateral tumours, of which eight showed the cardiovascular syndrome and six were malignant. Malignant tumours totalled 15 cases. Roth and others (1953) described three siblings with bilateral tumours. The tumours have weighed from 13 to 2,000 grams. In Mackeith's series nine had associated neurofibromatosis of von Recklinghausen.

In 1886 Fränkel described bilateral adrenal tumours and cardiac hypertrophy in a girl of 18 who had had, during life, attacks of palpitation, headache and vomiting. She had retinitis albuminurica and was diagnosed as a case of nephritis. He was surprised to find *post mortem* very slight alterations in the kidneys and a heart weight of only 320 g. The first clear clinical recognition of the syndrome was the paper of Labbé, Tinel and Doumer who, in 1922, described a woman of 28 who had attacks beginning with malaise followed by coldness, pallor and lividity of the extremities and face, then epigastric constriction, nausea and vomiting. The attacks lasted about three hours and were followed by tachycardia, flushing of the face, neck and chest, profuse sweating and extreme fatigue. She was thought to be a case of Graves' disease but six months later she was admitted to hospital for an attack of pulmonary oedema and it was noted that her systolic arterial pressure varied between 125 and 280 in a few hours. During the attacks the blood pressure was raised, but sometimes it was very high without an attack. The temperature was usually raised. She died in an attack of acute pulmonary oedema, and was found to have a chromaffin cell tumour of the left adrenal. The first successful operation was that of Mayo (1927). His patient was a woman of 30 who had had attacks for one and a half years lasting half to four hours, usually after breakfast or when moving in bed. The symptoms in the attack were palpitations, severe occipital headache, nausea, vomiting, choking sensation, dyspnoea, cough, a tight sensation in the chest, becoming painful, abdominal pain, coldness of the extremities, weakness, trembling, occasionally numbness and tingling of the extremities and blurring of vision. Prostration and abdominal distress followed. Between the attacks her blood pressure was 130/82. During the attacks she appeared anxious and her pupils were dilated. There was

our patients. The breathing may be increased in depth or rate or both. The neck veins are often distended and occasionally the thyroid swells. A coarse tremor occurs in some and shivering has been described. The pulse is small and may be fast or slow. Heart block, extrasystoles and pulsus alternans may occur. The most important sign, however, is the arterial pressure which may rise to extremely high levels, e.g. 300/180 mm. Hg during the attacks. Not infrequently the body temperature is raised during the attacks. A raised blood sugar and glycosuria are also described during attacks but may be absent. Howard and Barker noted that tetany had occurred in only one of their 18 cases, in which hyperventilation during the attack was a prominent feature; convulsions have not been described.

The attacks are of variable duration, from a few minutes to several days. After the attack the patient seems utterly exhausted and may enter a state closely resembling that of traumatic "shock" in which the pulse rate is fast and the blood pressure very low (van Goidsenhoven and Appelmans, 1934).

The patient may die in these attacks; usually of acute pulmonary oedema, occasionally of cerebral haemorrhage and occasionally of peripheral circulatory failure after the attack.

Many patients who have typical attacks have previously had slight attacks, e.g. of headache, dizziness and facial pallor, or of nausea and vomiting which may have been of the same nature. Conversely, some patients may experience notable rises of arterial pressure without noting any symptoms (e.g. the case of Labbé and others described above).

Difficulty of Diagnosis of the Paroxysms. In most of such cases the initial step in the diagnosis is the differentiation of the attacks, as described by the patient, from other similar attacks. The diagnosis is immensely simplified by observation of an attack, the pallor and coldness of the skin, the sharp rise of blood pressure and, occasionally, the engorgement of neck veins and swelling of thyroid.

... may occur in subjects with essential hypertension, may be associated with paraesthesia, palpitations, hyperpnœa, pain in various places, and cramps. In these attacks, too, the arterial pressure and pulse may rise. In patients whose arterial pressure is not initially high, the rise of arterial pressure is rarely extreme. But in patients whose initial pressure is already high, the rise of blood pressure may be very large. An important distin-

Swelling of the thyroid was noted by Barnett and others (1950) in two normal subjects who received intravenous infusions of noradrenaline, and in one of their cases of pheochromocytoma during the attacks. It was also noted in their cases by Bauer and Belt (1947) and by Strombeck and Hedberg, (1939).

are palpitations, thoracic and abdominal pain, nausea and vomiting, blanching and coldness of the skin and headache.

The attacks may begin with malaise, or with coldness or paræsthesia of the extremities, often beginning in the feet and passing up the body. One of the commonest first symptoms is palpitation but epigastric pain, sinking feeling or nausea, substernal pain or constriction, sneezing, throbbing in the temples, dizziness, headache or a coarse tremor may mark the onset of the paroxysm or occur at its height. The thoracic

TABLE 20.1. *Frequency of Occurrence of the Principal Symptoms in 18 Cases during Paroxysmal Hypertension (Howard and Barker, 1937).*

Symptoms	Number of cases
Blanched or mottled cold extremities	17
Palpitation	17
Nausea	16
Sweating	14
Vomiting	13
Headache	10
Pulmonary œdema	9
Precordial pain	8
Distention of neck veins	5
Dilated pupils	4
Body tremors	3
Dizziness	2

pain may closely resemble angina pectoris and be similarly associated with a sense of choking. Palpitations which may be slow (as with noradrenaline) or fast (as with adrenaline) are usual in the attack and in one of our patients (erroneously diagnosed formerly as hysteria) the forcible beating of the heart during nocturnal attacks was enough to waken the patient's wife. Nausea is described in nearly all attacks and vomiting in most. Sweating may occur in or after the attacks; lachrymation and salivation have been described. One of our patients had an intense feeling of alarm and a sensation of goose-skin during the attacks. Some patients become breathless in the attacks, and may cough up the pink frothy sputum of acute pulmonary œdema. During the attacks the patient is unable to pass urine, and in one of our patients micturition was interrupted at once if an attack began during the act.

If the patient is seen during the attack, he often appears anxious and the skin is blanched or mottled and cold. The pupils are dilated. Profuse sweating is not uncommon and goose-flesh occurred in one of

A man of 39 who had "suffered since the age of 33 from occasional momentary giddiness, even when sitting still, suggestive of the slightest form of minor epilepsy. Six months before he was seen these ceased and were replaced by peculiar and more prolonged attacks. First he felt a sensation of slight pricking in his hands and feet, combined with a cramp-like feeling; they became colder and colder, and his face grew pale. After about a minute he felt at the heart a peculiar sensation, intense fear and a feeling . . . was the sense of distress . . . was certain that he never lost consciousness. After about five minutes in all the attack gradually passed away."

(b) *Patients presenting with Hypertension in the Benign or Malignant Phases*

As has been noted the arterial pressure is persistently elevated between the attacks in a considerable fraction of the cases (11 of 18, Howard and Barker (1937), about half, Mackeith (1944), in four of six of our own cases at St. Mary's). Now in some of these patients, the attacks may be comparatively slight and have nothing in their content to suggest chromaffin tumour, and the patient may present as a case of benign or malignant essential hypertension. Such for example was the case reported by Green (1946) of a woman of 23 whose mother and sister both had hypertension and who presented with attacks of abdominal pain and vomiting. She had a variable blood pressure, the urine contained glucose and protein, and the fundi showed hypertensive neuro-retinopathy. The blood sugar curve was high, and she was treated for diabetes and controlled on 20 units of insulin daily. Since there was a depression and deformity of the upper pole of the left kidney, and massage of the left renal area raised the arterial pressure from 150/110 to 220/190, the abdomen was explored and a pheochromocytoma removed from above the left kidney. The arterial pressure remained normal for the six weeks of observation. In the case described by Thorn, Hindle and Sandmeyer (1944), a woman of 40 had had a systolic pressure of up to 120-130 in a normal pregnancy nine years before. Seven years before she had been . . . for . . . and . . . systolic arteriosclerosis. Ophthalmoscopic examination showed arteriosclerosis and white lines in the fundus. An amytal test reduced the arterial pressure from 240/110 to 100/60 . . .

... removed. Two . . . twenty days after operation the arterial pressure was

guishing feature of the attacks is that the skin usually feels hot rather than cold, and tends to be flushed rather than pale, but this is, unfortunately, not invariable.

(2) Menopausal hot flushes are rarely confusing as the attacks are slight and the skin is flushed. But the blood pressure tends to rise during them (unpublished observations).

(3) Hypoglycæmic attacks, nearly always occur long after a meal. They may closely resemble the attacks we have described. The patient notices weakness, sweating, tremor, and abdominal pain resembling hunger pains. More severe symptoms are numbness of the limbs, face and tongue, diplopia and difficulty in articulation. If more severe the patient may become comatose; fits occur in young children. These attacks, if witnessed, differ in that the skin is usually flushed rather than blanched. The blood sugar during the attack is very low rather than on the high side.

(4) Vaquez and Donzelot (1926) drew attention to the crises of breathlessness occurring with the laryngeal type of carcinoma of the œsophagus, and with primary lymphosarcoma of the mediastinum, in which the arterial pressure may rise by 70 to 100 mm. Hg, in this respect resembling chromaffin tumours.

(5) The type of angina pectoris described by Lewis (1931), occurring at rest in subjects with aortic regurgitation and associated with large rises of blood pressure and pulse rate. As I have seen them, these attacks resemble anxiety attacks both in the appearance of the patient and the circumstances precipitating them. The anginal pain is presumably an effect of increased cardiac work consequent on the rise of arterial pressure and pulse rate, together with poor coronary flow resulting from the low diastolic pressure of aortic reflux. During these attacks the patient's face is usually flushed.

(6) "Angina pectoris vasomotoria" of Nothnagel (1867) was most probably identical with the syndrome here discussed. Nothnagel described three males in their thirties or forties and one female aged 63 with no heart disease and enjoying good health between attacks. The symptoms in the attacks were anxiety, severe palpitation, giddiness, and numbness of the hands and feet. In one patient there was disturbed vision, in one clonic spasms of the limbs, in one a tearing pain in the left arm and in one a sense of suffocation. In all there was conspicuous blanching of the skin of the hands, feet and face. In one the pulse rate showed no change, in one it fell from 84 to 64. The attacks lasted fifteen minutes to one hour, and were produced by cold or alcoholic intoxication. It is particularly suggestive that a swelling of the neck developed in Case 2.

Some of the cases described by Gowers (1907) as vaso-vagal attacks would appear also to be of a similar nature, e.g. the following (Case 3).

tensive neuro-retinopathy, typical of malignant hypertension. Both patients had the adrenal tumour removed and a renal biopsy taken in one. In none of the histological sections, which I personally examined carefully, was any arteriolar necrosis found. Both had normal renal function, though one had red cells, casts and protein in the urine, and both continued to have high blood pressure after removing the tumour, though the pressure was reduced in one to such an extent that the neuro-retinopathy cleared up. The other required treatment with hexamethonium. Cahill (1948) described three cases of pheochromocytoma in children, two of whom each had two tumours. All three cases had hypertensive neuro-retinopathy; two had sustained hypertension. One of these patients died and no nephrosclerosis was found *post mortem*. In two cases removing the tumours abolished the hypertension during a short follow up.

Palmer and Castleman's (1938) case is worth quoting as it illustrates the development of persistent hypertension, with eventual hypertensive neuro-retinopathy, though no vascular lesions were found after death. A woman of 23 had for four years attacks which "started suddenly with a terrific, oppressive substernal pain associated with the feeling that she was choking to death and with the sensation of blood running from her head. This was followed by the onset of an agonizing generalized headache, marked shortness of breath and doubling up and contraction of the legs, arms and hands. She did not lose consciousness, but could not talk. The attack lasted about 10 minutes." Eighteen months before admission her blood pressure was 140/120 and urine was normal. Two months before admission her blood pressure was 210/130. On admission both optic discs were swollen, the retinal veins were engorged and there were many exudates. The blood pressure was 190/160 and the urine showed a trace of albumin. One attack was observed in hospital, the blood pressure rising from 250/150 to 300+/160 though the pulse remained at 60. Before the attack "her extremities were red, warm and relaxed. . . . During the height of the attack . . . the hands were irregularly blanched, cold and sweaty" This patient died in an attack. After death a right adrenal paraganglioma was found. "Both kidneys were normal in size and microscopically showed no vascular disease, as was true of the vessels in the other organs."

Only one case of pheochromocytoma associated *post mortem* with the renal changes of malignant hypertension has, to my knowledge, been reported (Platt and Davson, 1950); Platt (1954a) stated that this man behaved clinically exactly as a case of malignant hypertension: bilateral adrenal tumours were found *post mortem*. Urea retention has been described in some cases, but can be explained by the vomiting. In fact it would seem that in pheochromocytoma, alone of the tumours

140/88. Smithwick, Greer, Robertson and Wilkins (1950) analysed the findings in 11 cases in which a phaeochromocytoma was found at operation for sympathectomy, the diagnosis not having been made before. The chief findings are summarized in Table 20.2 where they are compared with the findings in 107 cases of phaeochromocytoma reported in the literature and with the findings in 100 consecutive unselected cases of essential hypertension attending Smithwick's clinic. They emphasize the frequency of excessive sweating, vasomotor phenomena, an elevated body temperature, an elevated BMR and

TABLE 20.2. *Symptoms, Signs and Findings suggestive of Phaeochromocytoma in Patients with Persistent Hypertension* (Smithwick and others, 1950).

Symptoms and signs	Incidence in 11 phaeochromocytomas observed Per cent.	Incidence in 107 phaeochromocytomas reported Per cent.	Incidence in 100 cases of essential hypertension Per cent.
Excessive sweating . . .	90	52	2
Vasomotor phenomena . . .	90	47	0
Elevated temperature . . .	78	70	10
Normal cold pressor response .	73	63	22
Fasting blood sugar > 120 mg.	64	61	13
BMR > + 20 per cent. . . .	60	57	5
Postural tachycardia	55	—	15
Postural hypotension	44	50	3
Glycosuria	36	50	4
Paroxysmal attacks	36	75	0

glycosuria in phaeochromocytoma, and their rarity in essential hypertension. Paroxysmal attacks were present in only one-third of their patients. Of our six patients with phaeochromocytoma only one was entirely unsuspected. She was a red-faced woman of 49 who presented with a moderate hypertension and a tumour emerging from under the left costal margin which was thought to be the spleen till it was excised surgically; it was found to be a phaeochromocytoma containing 0.3 mg. 1-adrenaline and 10 mg. dl-noradrenaline per gm. of tumour tissue (Case III of Holton, 1949). Her past history, however, revealed attacks of palpitation, thumping at the back of the head and profuse sweating. Her hypertension persisted after removing the tumour.

(c) *The Malignant Phase in Chromaffin Tumours*

Of our six cases of phaeochromocytoma, two, both with persistent hypertension and paroxysmal hypertension, presented with hyper-

pressure on intravenous injection of the drug. Goldenberg and Aranow (1950) reported that 59 patients with operatively demonstrated phaeochromocytomas had shown positive tests, while only three false negative tests had been observed. They showed that when arterial pressure was raised by infusing noradrenaline or more especially adrenaline, an intravenous injection of piperoxane would abolish the rise. Others have had less encouraging experiences. Thus Prunty and Swan (1950) failed to show any reduction by piperoxane of the arterial pressure raised by infusion of noradrenaline in normal subjects. In the experience of my hospital (Hamilton and others, 1953), the test was negative in two, and positive in only one case of proved phaeochromocytoma. Piperoxane, unfortunately, also produces a pronounced rise of arterial pressure in some subjects with hypertension and cannot be regarded as entirely without risk (Emlet and others, 1951). Grimson and others (1949) introduced another adrenolytic drug C-7337 or regitine, which produces very little change in the arterial pressure in essential hypertension. Emlet and others (1951) found positive responses both to piperoxane and regitine in four patients with phaeochromocytoma, but the responses to regitine were longer and more easily distinguished from the transient falls sometimes encountered in patients with essential hypertension. They also found that both piperoxane and regitine produced significant falls of blood pressure in five patients with hypertension and uræmia and no phaeochromocytoma. Goldenberg (1954) has also encountered patients with phaeochromocytoma in whom negative responses to both piperoxane and regitine were observed.

Pharmacological tests for the presence of phaeochromocytoma are thus fallible, and, in my view, add very little to the case for or against a phaeochromocytoma, built up on the clinical history, examination and radiological investigations. Fortunately, these tests have been, or will be, quite superseded by a method of great precision, namely, the assay of catechol amines in the urine.

Urinary Excretion of Adrenaline and Noradrenaline

Engel and v Euler (1950) showed that the rate of urinary excretion of adrenaline and particularly noradrenaline was greatly raised in certain cases of phaeochromocytoma. In the method, as improved by v Euler and Hellner (1951), the amount of noradrenaline excreted in 24 hours is usually above the normal in all cases of phaeochromocytoma.

phaeochromocytoma
noradrenaline

usually excretion of

of hypertension here considered, there is a dissociation between the clinical sign, hypertensive neuro-retinopathy, and the histological sign, arteriolar necrosis, of malignant hypertension. This is perfectly understandable on the hypothesis here presented to explain those lesions (Chapters 11 and 12), since the mechanisms by which they seem to be produced are not quite identical.

DIAGNOSIS OF CHROMAFFIN TUMOURS

The presence of a chromaffin tumour is suspected from the history of the attacks, and is almost certain if, in addition, the patient is seen in an attack, and is found to have gross elevation of the arterial pressure with blanching and coldness of the skin. Other clinical features and the differential diagnosis of the attacks have been considered. If the patient has a convincing history and has, in addition, a palpable abdominal tumour of suitable characteristics, or has a low kidney with radiological evidence of a soft tissue mass in the region of the adrenal gland, then the diagnosis is sufficiently probable to justify operation, with the expectation of finding and excising a chromaffin tumour.

In many cases, however, the history is far from convincing; no attack is available for observation, and the evidence of an abdominal tumour is equivocal. An intermittent glycosuria and a raised B.M.R. are not more than suggestive. Clearly, in such cases, some much more reliable index is needed. Two lines of attack have been followed, pharmacological tests and urinary assay of pressor amines. Of these the latter is undoubtedly the method of choice.

Pharmacological Tests

Roth and Kvale (1945) found that intravenous injection of 0.025 to 0.050 mg. histamine base produced a typical attack in proved cases of phaeochromocytoma with a rise of pressure about 100 mm. Hg above that produced by immersing the hand in cold water. The test was based on the experimental evidence suggesting that intravenous injection of histamine released adrenaline from the adrenal glands. In normal patients or patients whose phaeochromocytoma had been removed, the rise of blood pressure was less than that produced by immersing the hand in cold water. This test has been used frequently since, mostly with good success, but occasionally with failure (for references see Entwistle and others, 1951). Its disadvantage is that the attacks are dangerous and therefore I, personally, have never used it.

The use of adrenergic blocking agents was suggested by Biskind and others (1941) but was first popularized by Goldenberg, Snyder and Aranow (1947), who used F 933, Benzodioxane, or Piperoxane (0.25 mg. per kg. intravenously). Subjects with hypertension due to circulating adrenaline or noradrenaline should show a significant fall of blood

naline, the less the probability that the tumour was actually adrenal. Hamilton and others (1953) and Goldenberg (1954) however, report suprarenal tumours containing a large excess of noradrenaline.

v. Euler, Hellner and Purkhold (1954) measured the noradrenaline excretion in 500 cases of hypertension "of unknown origin, selected at random, but corresponding to the 'essential' group." In about 80 per cent, the excretion was less than 57.6 μ g. per twenty-four hours, i.e., within the normal range. In 17.4 per cent, the excretion ranged from 57.6 to 86.4 μ g, values not regarded as significantly increased. In 16.4 per cent, the excretion, greater than 86.4 μ g. per twenty-four hours, was regarded as definitely increased. The table of age distribution, which they give, shows that the frequency of the higher rates of excretion rises with age. Now this was precisely what was found by Burn (1953) in his control subjects. Until, therefore, we have comparable figures for control subjects of similar age, it would be unsafe to conclude that, in a substantial proportion of patients with essential hypertension, there was an increased production of noradrenaline, presumably from sympathetic nerves; though this, of course, is the interesting possibility raised by these data.

The Maximal Heat Elimination from the Hand

The blood flow through the hand may be simply estimated calorimetrically by the heat elimination. When one or more of the other limbs is immersed in hot water, the heat elimination rises to a maximum that cannot be further increased by anaesthetizing the mixed nerves to the hand. This maximal heat elimination thus represents hand blood flow when sympathetic vasomotor tone has been removed (Pickering, 1936b). Hamilton and others (1953) found the maximal heat elimination greatly reduced in four out of five pheochromocytomas, even though no attack was present; in all four the heat elimination was restored to normal after excising the tumour. This is a simple test, probably without risk, but it is, of course, inferior in precision to the excretion of pressor amines.

Locating the Tumour

If it is known from the above data that a chromaffin tumour is present, it is necessary to locate it. The tumour, or a low kidney, may be felt. A plain X-ray of abdomen may reveal a soft tissue mass in the region of the adrenal, or an intravenous pyelogram show distortion and displacement of the kidney. Perirenal air insufflation may be used if necessary but is not devoid of risk of air embolism (Blackwood, 1951) or of precipitating a severe paroxysm (Mackeith, 1944); the pre-sacral route is the safest. If in doubt, it is better surgically to explore the abdomen transperitoneally, examining the right side

toma, and is well above the level found in essential hypertension in the experience of most authors (Hamilton and others, 1953; Burn, 1953; Goldenberg, 1954). With the introduction of chemical methods of estimating these substances (see, for example, Goldenberg, 1954), there seems little doubt that the urinary excretion of the catechol amines will become the standard method of deciding whether or not a phæochromocytoma is present.

TABLE 20.3. *Urinary Excretion (μ g. per Twenty-four Hours) of Adrenaline and Noradrenaline.*

Authors	Normal		Essential Hypertension		Phrochromorytoma	
	A.	N.A.	A.	N.A.	A.	N.A.
v. Euler and Hellner (1951).	11.5 ± 6	29.0 ± 12.3	Combined A. & N.A. up to 70 (28 cases) N.A. only. Less than 57.6 µg. in 66 per cent. 86.4 - > 173 in 16 per cent. of 500 cases. N.A. mean 80.		13-780	113-1800
v. Euler (1951b)					(six cases)	
Hamilton and others (1953).	412 to 4,375 (five cases)					
v. Euler, Hellner and Parkhold (1954).						
Burn (1953)	18.0 (age 3 months to 10 years)	180 to 3,800 (three cases)				
	71.0 (age 41 to 63 years)					
Goldenberg (1954)	14 to 41 (13 subjects)	41* to 425* to 456 890				
		7 to 100 (35 subjects)				

* Chemical Assay. The remaining figures were by bio-assay.

v. Euler found that the ratio of noradrenaline to adrenaline was very much the same in the urine and in the tumour in a given case. Hamilton and others (1953) confirmed this. v. Euler also found that in his series, the adrenaline formed from 1 to 58 per cent. of the pressor amine content of the tumour. The three tumours containing a great excess of noradrenaline were situated outside the adrenal gland, while those containing a smaller excess of noradrenaline, or an excess of adrenaline, were anatomically closely connected to the adrenal. Now the normal human adrenal contains 84 ± 5.3 per cent. of adrenaline (v. Euler, Franksson and Hellström, 1954). He therefore suggested that the ratio of adrenaline to noradrenaline in the urine might be of use in locating the tumour; the greater the predominance of noradre-

Mary's (Barnett and others, 1950, Hamilton and others, 1953, Peart, 1954), three had persistent hypertension between the attacks before operation. All three continued to show persistent hypertension after removal of the tumour, though the attacks were abolished in all and, in the only two in which the excretion of pressor amines was measured, this had returned to normal (Hamilton and others, 1953). In one of those patients the hypertension continued to be so severe that treatment with hexamethonium compounds was necessary. We are thus inclined to think that pheochromocytoma provides yet another example of the theme so often recurrent in this work, namely that removal of the prime cause does not always abolish the hypertension. It is a pity that so few cases have been adequately followed up, so that this question is still in doubt.

Some few of these tumours are malignant, and cannot be removed, or recur. Radiotherapy is usually employed with, at least temporary, success.

MECHANISM OF THE HYPERTENSION IN CHROMAFFIN TUMOUR

The demonstration of the presence of adrenaline in the tumours, reported by Labbé, Azérad and Violle (1929) and by Rabin (1929), and by many subsequent workers, at once seemed to provide the explanation of these attacks. Beer, King and Prinzmetal (1937) seemed to provide the final evidence by showing that a vasoconstrictor substance was present during the paroxysms, and absent after removing the tumour, in one case, and that this substance resembled adrenaline, in that its action on biological assay was abolished by ergotoxine. However, there was a real difficulty, namely, that infusion of adrenaline into man usually produced no rise of diastolic pressure and, almost invariably, a quickening of the pulse; while in paroxysmal hypertension, the diastolic pressure usually rises greatly in attacks, and in some patients the pulse slows. The dilemma was resolved by Holton's (1949) finding, subsequently confirmed (see Table 20.4), that the chromaffin tumours contain very large excesses of noradrenaline and adrenaline but particularly the former.

The actions of adrenaline and noradrenaline on man have been considered already (Chapter 6). Here it will suffice to note that Barnett and others (1950) found that the circulatory changes induced by infusing noradrenaline into normal subjects almost always showed the following characteristics:—

in man, the pulse rate slows in the attack, and that the opposing effects balance with mixtures containing three or eight parts of noradrenaline for each part of adrenaline. As a rough guide it may therefore be said that if the pulse rate slows in the attack,

first because of the predominance of right adrenal tumours, but not forgetting that the tumour may be outside the adrenal and not very large. Naturally, the pre-aortic region is most carefully explored. I have had one case in which the diagnosis based on the nature of the attacks and the urinary excretion of pressor amines seemed certain but in which Mr. Dickson Wright explored both sides of the abdomen and the pelvis without finding a tumour and in which radiological examination of the chest was negative.

THE EFFECTS OF EXCISING THE CHROMAFFIN TUMOUR

As van Goidsenhoven and Appelmans (1934) pointed out, these tumours, if left in the body, are usually fatal. The object of treatment is therefore to remove the tumour, or tumours, surgically. This operation is full of hazards which should be anticipated and, if possible, avoided. The chief hazard is the production of a fatal paroxysm by the mobilization of the tumour, even though it is handled with extreme gentleness. Barnett and others (1950) found the pressor action of noradrenaline greatly enhanced by atropine, which should, accordingly, never be given, preoperatively, to these patients. The pressure should be recorded during the operation and, if it rises, 5 to 10 mg. regitine should be injected intramuscularly in the hope of reducing it, further injections being given each hour if the pressure rises. A similar dose is sometimes given before the tumour is mobilized, even if no rise of blood pressure has occurred. Intravenous digoxin may be necessary if acute pulmonary oedema or pulsus alternans supervene.

When the last haemostat is applied to the tumour, the arterial pressure usually falls precipitously, and the patient may pass into a state of circulatory failure from which he, or she, may not recover. It is now urgently necessary to maintain arterial pressure at about the levels of 120/80 by intravenous infusion of 1-noradrenaline, 10 or 20 mg. being added to a litre of saline and the rate adjusted to maintain the pressure. In some instances, the patients become relatively refractory and large doses of noradrenaline are needed.

In the vast majority of patients who have paroxysms of hypertension, removing the tumour abolishes the attacks. But in 16 of Mackeith's 165 cases bilateral tumours were present. As Roth and others (1953) have pointed out, bilateral tumours may be familial. In such cases removing the second tumour abolishes the attacks.

It is generally stated in published works that persistent hypertension is also abolished by excising the tumour. However, in nearly all the recorded cases (Thorn, Hindle and Sandmeyer, 1944; Green, 1946; Cahill, 1948; Swan, 1951; van Goidsenhoven and Appelmans, 1934; Howard and Barker, 1937; Biskind, Meyer and Beadner, 1941; Mackeith, 1944) the follow-up is very short. Of our six cases at St.

Mary's (Barnett and others, 1950, Hamilton and others, 1953, Peart, 1954), three had persistent hypertension between the attacks before operation. All three continued to show persistent hypertension after removal of the tumour, though the attacks were abolished in all and, in the only two in which the excretion of pressor amines was measured, this had returned to normal (Hamilton and others, 1953). In one of those patients the hypertension continued to be so severe that treatment with hexamethonium compounds was necessary. We are thus inclined to think that pheochromocytoma provides yet another example of the theme so often recurrent in this work, namely that removal of the prime cause does not always abolish the hypertension. It is a pity that so few cases have been adequately followed up, so that this question is still in doubt.

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140 systolic and 60 to 80 diastolic. In the second place in three of our cases with persistent hypertension, removing the tumour did not abolish the hypertension though in two, urinary excretion returned to normal (Hamilton and others, 1953). Finally, in rabbits we were completely unable to produce hypertension sustained for several days by continued intravenous infusion of adrenaline, noradrenaline, or mixtures of the two (Blacket, Pickering and Wilson, 1950), using the same technique which had produced sustained hypertension with renin. We did note that after stopping the infusion there was a profound fall of arterial pressure to well below initial levels, and this we attributed (but without direct evidence) to release of vasodilator substances. It is of very great interest that an exactly similar phenomenon has been described after sustained adrenaline infusions in man (Green, Johnson, Lobb and Cusick, 1948). Moreover, as has been noted, great lowering of blood pressure occurs after severe attacks of paroxysmal hypertension, and after surgical removal of the tumour. Quite obviously, mechanisms tending profoundly to oppose the rise of blood pressure are evoked by the continued presence of large amounts of adrenaline and noradrenaline in the blood.

It would seem much more probable that the sustained hypertension of pheochromocytoma is the permanent legacy to the cardiovascular system, of repeated hypertensive attacks evoked by the pressor amines. Examination of case histories such as that of Palmer and Castleman (1938) (p. 405) offers some support for this suggestion, which, however, breaks down in detail. However, the information at present available is fragmentary in the extreme, a history of subjective symptoms, a record of arterial pressure over a few days or weeks, a single assay of urinary pressor amines, a follow-up of a few weeks after removing the tumour, being the sum total of data in most cases.

The reader may feel that a disproportionate amount of his time has been dissipated over the consideration of a rare disease. The writer would accept the reproof, but he would urge that this is the one and only example of hypertension in which we have even a remote acquaintance with the mechanism. From this condition we can yet learn much that may illuminate the whole subject, but many more data and a much more critical approach to these data are needed.

SUMMARY

The paroxysms of hypertension that

... amounts of noradrenaline and adrenaline, the patients excrete excessive amounts of these substances in the urine, and the attack

the tumour contains over 75 per cent. of noradrenaline. Barnett and others (1950) found that the subjective effects of adrenaline were much greater than with the same dose of noradrenaline. With the former anxiety, trembling and palpitations are notable, with the latter comparatively slight. These features may help as a guide to the composition of the tumour, but doses producing effects comparable to those seen in natural paroxysms have never been given to normal subjects for obvious reasons.

TABLE 20.4. *Content of Adrenaline and Noradrenaline (mg. per g.) of Normal Adrenal Glands and Phæochromocytoma.*

Authors	Normal Glands			Phæochromocytoma		
	Weight g.	Adr.	N. Adr.	Weight g.	Adr.	N. Adr.
v. Euler (1951b)				6-200	0.05-2.3	0.75-8.4
Hamilton and others (1953).				(6) 46-680	1.6-4.7	
Holton (1949)				(5) ?	0.3-4.0	6.0-11.0
Goldenberg and others (1950).				(3) 21-780 (20)	0.03-0.1	0.95-8.8
v. Euler Franksson & Hellstrom (1954).	4.2-10.5 M = 5.9	0.22-0.84 M = 0.49 ± 0.18	0.044-0.16 M = 0.090 ± 0.041			

The final evidence that the paroxysms are due to the release of adrenaline and noradrenaline is that they cease when the tumour is removed. Urinary assay suggests that the release of adrenaline and noradrenaline from the tumour occurs more or less continuously into the blood stream, even in the absence of attacks, and even with a normal arterial pressure. This accords well with the finding of a reduced heat elimination from the hand. Presumably the concentration of the amine in the blood is enough to constrict the hand vessels but not enough to raise arterial pressure. In the attacks the output is enormously increased, as is again confirmed by urinary assay (Hamilton and others, 1953).

While the relationship of the paroxysms of hypertension to the discharge of amines from the tumour seems clear enough, the causation of persistent hypertension is quite obscure. It is usually assumed that the hypertension is due to circulating adrenaline and noradrenaline, but our evidence is quite opposed to this view. In the first place, in cases four and five of Hamilton and others (1953) the urinary excretions of pressor amines were respectively 500 and 412 µg. per day, yet case four had a pressure, between attacks, of 200 to 230 systolic and 120 to 150 diastolic, while the corresponding figures in case five were 120 to

CHAPTER 21

CUSHING'S SYNDROME

IN 1932, Cushing described a curious syndrome which he thought was due to basophil adenoma of the pituitary gland. Subsequent work has shown that the pathology of the condition is by no means simple, and that the effective disturbance is one concerning the steroids secreted by the adrenal cortex. High blood pressure is one of the cardinal features of this syndrome, and it would seem not unlikely that a careful study of the condition might yield information of great importance to our central problem

CLINICAL FEATURES

In his original paper, Cushing collected a group of 12 cases, all young adults presenting the following features: (1) a rapidly acquired and often painful adiposity confined to face, neck and trunk, (2) a dusky or plethoric appearance of the skin with purplish striae, (3) an increased growth of hair on the beard area and trunk in females and pre-adolescent males, (4) a tendency to loss of stature and kyphosis due to softening of the vertebrae, (5) sexual dystrophy as shown by amenorrhoea in the female and impotence in the male, (6) raised arterial pressure (178/100 to 230/170), (7) a tendency to polycythemia, (8) backache, abdominal pain and (9) fatigue and, ultimately, extreme weakness. The malady was associated with an increased susceptibility to infection, of which died eight of the nine cases coming to post-mortem examination.

Many examples of this very striking and, to the patient, very disconcerting condition have since been described. Plotz, Knowlton and Ragan (1952) have reviewed the chief features of 33 cases collected at the Columbia Medical Centre, New York, and 189 cases reported by others. Females predominated over males in the ratio of three to one. In the Columbia series the age range was 11 to 51 years, but younger patients have been described. Of the 32 cases followed, 17 died after an average of four and a half years of known disease, the remaining 15 remaining alive at an average of nine years from the onset.

The chief symptoms and signs are summarized in Table 21.1. Of these, the outstanding symptoms are obesity, particularly of face, neck and trunk, plethoric appearance of the face, hirsuties, purple striae particularly on the belly, buttocks and round the shoulder girdle, acne

abolished by excising the tumour or tumours. Moreover, all the known phenomena of the attacks can be reproduced by infusing noradrenaline intravenously in normal subjects.

In some cases, particularly of long duration, the arterial pressure is raised between attacks, and in yet others the attacks are inconspicuous or absent. Such cases can only be diagnosed with certainty by the demonstration of an abnormal urinary excretion of noradrenaline and adrenaline. In some of these cases, excising the tumour may abolish the attacks, and reduce the urinary excretion of pressor amines to normal, and yet the hypertension continues. It seems, therefore, that here is another example of sustained hypertension due to a specific lesion that is not fully reversible when the original lesion is removed.

The syndrome of the malignant phase of hypertension may also occur with chromaffin cell tumours. Neuro-retinopathy has, however, been recorded much more frequently than arteriolar necroses.



FIG 21-1 Cushing's syndrome before and after subtotal adrenalectomy.

(a) December, 1951. Age 23. Note obesity of face, neck and trunk, high skin colour of face, purple striae and extreme weakness. Blood pressure 200/130.

(b) December, 1952. Blood pressure 125/80. Eight months after removal of whole of one and threequarters other adrenal by Prof. C. Rob. Cortisone discontinued two weeks after operation. Patient subsequently married, in 1954 became pregnant and was delivered of a normal

menstrual disturbances (in females), impotence (in men), weakness and backache. Mental disturbances, ranging in severity from irritability to major psychosis, occurred in two-thirds of the patients in the Columbia series.

The appearance of the patient confirms the change that she (or he) has noticed and is often characteristic (Fig. 21.1a). Hypertension, with or without cardiac enlargement, and varying in severity from mild to the severe degree associated with the malignant phase, is usual.

TABLE 21.1. *Symptoms and Signs in Patients with Cushing's Syndrome*
(Plotz, Knowlton and Ragan, *Amer. J. Med.*, 1952, 13, 597).

Symptoms or Signs	Columbia Series Per cent. (33 Cases)	Previously Reported Per cent. (189 Cases)
Obesity	97	97
Hirsutism	73	69
Hypertension	84	85
Amenorrhœa	86	71
Oligomenorrhœa		
Impotence in men		
Plethoric appearance	89	50
Purple striae	60	71
Mental symptoms (major 24 per cent.) (minor 43 per cent.)	67	31
Poor wound healing or severe infection	42	30
Weakness and backache	83	50
Acne, skin pigmentation or other rash	82	26
Purpura or easy bruisability	60	23
Ankle edema	60	28
Headache	58	34
Neurologic symptoms or signs	39	17
Polydipsia or polyuria	39	25
Virilism	11	5
Exophthalmos	11	8

Decalcification of the skeleton is a striking feature on radiological examination, and is probably accountable for the shrinkage in stature, and the back and limb pains, which are common features of the disease. Of five cases investigated in St. Mary's Hospital, Strickland (1954) found fractures of the ribs in all, fractures of the pubic rami in three, fractures of the vertebral bodies in two, and fracture of the femoral neck in one. This is a much higher incidence of pathological fractures than hitherto reported. But since these fractures may be painless and unsuspected clinically, the importance of a radiological survey of the whole skeleton is emphasized. In conformity with the skeletal changes,

TABLE 21.2. Laboratory Data in Thirty-three Patients with Cushing's Syndrome (Plotz, Knowlton and Ragan, Amer. J. Med., 1952, 13, 597).

		Range	Over-all Average
Red blood cell count	48% above 5.0 million/mm ³	3.4-6.0	5.02
White blood cell count	48% above 10,000/mm ³	5,800-15,000	10,050
Eosinophiles	79% below 100/mm ³	- 37- + 32	57
Basal metabolic rate (32 cases)	7% above + 20	8-51	24%
	20% below - 20	81-300	116
24-hour uptake of radioactive iodine (5 cases)	49% above 100 mg %		100
Fasting blood sugar	Present in 94%	90-11.3	30
Diabetic glucose tolerance (31 cases)	Present in 15%	22-4.4	269
Frank diabetes		147-460	10.8
Serum calcium (28 cases)	39% above 250 mg. %	0-20.6	17.8
Serum phosphorus (25 cases)	20 females	15.1-20.2	3.87
Cholesterol (28 cases)	5 males	0.80-0.3	5.02
24-hour 17-ketosteroid excretion (25 cases)	Formaldehydogenic method (Normal 0.5-1.5)		
	Phosphomolybdic acid method (Normal 2-4)		
24-hour 11-oxy steroid excretion (6 cases)	Present in 27%		
	Present in 50%		
Glycosuria	37% below 100.0 mEq./L.	21.2-40.2	29.5
Albuminuria		78.1-107.4	99.0
Serum carbon dioxide content-mEq./L. (27 cases)		130.0-147.0	142.7
Serum chlorides-mEq./L. (14 cases)		3.2-5.3	4.2
Serum sodium-mEq./L. (11 cases)			
Serum potassium-mEq./L. (11 cases)			

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		Range	Over all Average
Red blood cell count	48% above 5.0 million/mm ³	3.4-6.0	5.02
White blood cell count	48% above 10,000/mm ³	5,800-15,000	10,050
Eosinophiles	79% below 100/mm ³		57
Basal metabolic rate (32 cases)	7% above + 20	- 37 - + 32	- 6
	20% below - 20		
24-hour uptake of radioactive iodine (5 cases)	49% above 100 mg %	8-51	24%
Fasting blood sugar	Present in 91%	61-300	110
Diabetic glucose tolerance (31 cases)	Present in 15%		
Frank diabetes			
Serum calcium (28 cases)		9.0-11.3	10.0
Serum phosphorus (25 cases)		22-4.4	3.0
Cholesterol (28 cases)	39% above 250 mg %	147-460	203
24-hour 17-ketosteroid excretion (25 cases)	20 females	0-20.6	10.8
	5 males	15.1-26.2	17.8
24-hour 11-oxyteroid excretion (6 cases)	Formaldehydogenic method (Normal 0.5-1.5)	0.80-6.0	3.87
	Phosphomolybdic acid method (Normal 2-4)		5.02
Glycosuria	Present in 27%		
Albuminuria	Present in 50%		
Serum carbon dioxide content-mEq./L. (27 cases)		21.2-46.2	29.5
Serum chlorides-mEq./L. (27 cases)		78.1-107.4	99.6
Serum sodium-mEq./L. (14 cases)	37% below 100.0 mEq./L.	136.0-147.0	142.7
Serum potassium-mEq./L. (11 cases)		3.2-5.3	4.2

nephrocalcinosis, and renal calculi are not uncommon (Kepler and Locke, 1950). Albright (1943) has attributed the changes in the skin (redness and purple striae) to atrophy of the skin, a conclusion with which I agree, and the changes in the skeleton to a deficiency in the protein matrix of bone.

Laboratory Findings

The laboratory findings in the 33 patients of the Columbia series are summarized in Table 21.2. Of these changes the following are worthy of comment. Polycythemia is not an invariable feature as Cushing supposed; the plethoric appearance would seem to be due more to thinning of the skin and vasodilatation of the minute vessels, than increased haemoglobin content of the blood. The eosinophils tend to be reduced.

Diabetes is present in a minority but a glucose tolerance curve of the diabetic type is present in nearly all. The excretion of 17-keto-steroids (which includes the androgen fraction) may be low, normal or high. The 11-oxysteroids, as determined by the formaldehydogenic method, are usually, but not always, increased. Sprague and others (1953) have pointed out that it is not possible to distinguish between tumours of the adrenal cortex and cortical hyperplasia by estimating either of these steroid fractions in the urine. It is usual to find a raised CO_2 content, and a reduced content of chloride and potassium in the serum—in the technical jargon of the day, hypochloræmic, hypokalmæmic alkalosis!

The Hypertension of Cushing's Syndrome

There are, unfortunately, few systematic observations on the behaviour of the circulation in Cushing's syndrome from which one may hazard a guess as to the nature of the circulatory fault. In one case I found (Pickering, 1936b) the blood flow through the hand was within the normal range, after cutaneous vasomotor tone had been removed. It would seem, therefore, that a non-nervous vasoconstriction is present.

In 1934, MacMahon, Close and Hass described two patients with Cushing's syndrome, in whom the *post mortem* findings were those of malignant hypertension, with acute necrosis of small arteries and arterioles in the usual distribution. Since then, many cases have been described in which the clinical course characteristic of malignant hypertension with rapid renal failure occurred. On the whole, these patients tend to have a severe hypertension. It is also known that when removal of an adrenal cortical tumour or subtotal adrenalectomy succeeds in lowering arterial pressure persistently, the neuro-retinopathy recedes and renal function remains stable. The behaviour of

high blood pressure in Cushing's syndrome is, thus, in general conformity with the thesis advanced earlier, namely, that the malignant phase is an expression of a very severe hypertension.

THE HORMONAL BASIS OF CUSHING'S SYNDROME

Of Cushing's original 12 cases, a basophil adenoma of the pituitary gland was present in three and other pituitary adenomata in three others. However, it soon became clear that small basophil adenomas, similar in size to those described by Cushing, were not uncommon, various kinds of small adenomata occurring, for example, in about 10 per cent of glands collected at routine autopsy (see Cushing, 1932). Before that, Leyton, Turnbull and Bratton (1931) had described a similar case in which a cancer of the thymus was found *post mortem*. Later, several cases were described with benign and malignant tumours of the adrenal cortex. Finally, there are a very few cases on record in which other tumours, e.g. carcinoma of pancreas and sympathicoblastoma, have been present (see Plotz and others, 1952).

Crooke (1935) was the first to attempt to bring order out of this chaos. Stimulated by a chance observation, he examined the pituitaries of 12 cases, six of which had pituitary basophil adenomas, three of which had had thymus tumours, and the remainder tumours or hyperplasia of the adrenal cortex. In each case he found a characteristic change in the basophil cells of the pituitary. "The normal cytoplasm charged with ripe basophil granules is replaced by a dense homogeneous hyaline cytoplasm." In a series of control observations, he found a very slight amount of hyaline change in two cases of high blood pressure associated with Bright's disease, but the hyalinization was absent from 61 other cases of high blood pressure with or without Bright's disease, from seven basophil adenomata coming from patients who had not displayed Cushing's syndrome, and from one case of virilism due to a carcinoma of the suprarenal cortex. Crooke's observations have been confirmed in the main; in the cases collected by Plotz, Knowlton and Ragan (1952) hyalinization of the pituitary basophil cells was found in all but four of 97 cases in which adequate histological data were available.

The cure of several cases by removal of a tumour of the adrenal cortex, and the frequent presence of adrenal hyperplasia, strongly suggested that, whether or not the primary disturbance was in the pituitary, the chief site of production of the responsible hormones was the adrenal. This suspicion has been greatly strengthened by the observation that many of the features of Cushing's syndrome are

cortisone when administered in sufficiently high dosage for a protracted period to induce most of the clinical and metabolic features of Cushing's syndrome was demonstrated. The features so induced in varying combinations included rounding of the facial contour, hirsutism, acne, keratosis pilaris, muscular weakness, edema, amenorrhea, cutaneous striae, mental depression, impairment of carbohydrate tolerance, negative nitrogen balance, increased excretion of corticosteroids in the urine and hypochloremic hypopotassemic alkalosis. Significant hypertension was observed in only 1 case, in which the patient probably had antecedent parenchymatous renal disease."

At the present time there is evidence that three types of steroid hormone are secreted by the human adrenal cortex, although the evidence is not as complete in man as in experimental animals. These hormones are :—

(1) A hormone influencing the metabolism of sodium, potassium and chloride now called Aldosterone (Simpson and others, 1953) which in various assay methods for this type of hormonal activity has an activity thirty to 100 times that of desoxycorticosterone (Simpson and Tait, 1953 ; Mach and others, 1954). This hormone has been isolated from ox and hog adrenal gland extracts (Wettstein, 1954), from adrenal venous blood in the dog and monkey (Simpson, Tait and Bush, 1952) and in the rat (Singer and Stack-Dunne, 1954), from the urine of patients with various types of oedema (Luetscher and Johnson, 1953, 1954) and with pregnancy toxæmia (Venning, Singer and Simpson, 1954) and its presence demonstrated in the peripheral plasma of normal human subjects (Simpson and Tait, 1955).

(2) Hormones influencing the metabolism of proteins, carbohydrates, fats, purines, calcium and certain aspects of the metabolism of salt and water. In man these are hydrocortisone and a variable amount of corticosterone (Mason and Sprague, 1948 ; Nelson and others, 1951 ; Sweat and others, 1953 ; Bush, 1953a and b ; Romanoff, Hudson and Pincus, 1953).

(3) Hormones having androgenic activity of which 11β -hydroxy-androstenedione is the principal secretory product in man (Salamon and Dobriner, 1952 ; Romanoff and others, 1953).

In addition, oestrogens and progesterone have been isolated from extracts of ox adrenals, but there is no evidence proving that they are secreted by the human adrenal.

The hormonal disturbance of Cushing's syndrome is complicated and varies from patient to patient ; and it is only recently that methods capable of determining the nature of the disturbance have been evolved. In most patients with this disease all the older methods indicated an increased rate of excretion of active adrenal steroids, or of substances believed to be their metabolites (Sayers, 1950) and studies with more

recent and reliable methods (Lieberman and Teich, 1953) have, on the whole, confirmed these earlier findings (Sweat and others, 1953).

Again, it has been possible to demonstrate with the new techniques that the concentration of hydrocortisone and its metabolites in peripheral plasma is increased in such patients (Sweat and others, 1953).

In some cases an increased excretion of those metabolites known to be derived from 11β -hydroxyandrostenedione (Dorfman and Ungar, 1953) has been demonstrated (Rubin, Dorfman and Pincus, 1954). In some cases of the disease, and in all patients with the adrenogenital syndrome, there has been evidence that the relative proportions of the normal hormones are greatly altered; and that steroids not normally secreted by the adrenal cortex in more than trace quantities have been secreted in large quantities by the adrenals of some of these patients (Lieberman and Teich, 1953, Dorfman and Ungar, 1953). These changes have been observed particularly in those patients showing clinical features intermediate between those of Cushing's and the adrenogenital syndrome, those with adrenal tumours, and those with congenital bilateral adrenal hyperplasia.

If attention is limited to those cases showing the typical picture of Cushing's syndrome, namely those in which the metabolic disturbances predominate, and virilism is the accompaniment rather than the principal feature of the disease, then it seems correct at present to describe the adrenal disturbance of the disease as an increased rate of secretion of all the adrenocortical hormones by the gland, in the proportions normal for the individual before his or her disease. This increase, in the absence of an adrenal tumour, is secondary to an increased rate of secretion of the adrenocorticotrophic hormone (ACTH) by the pituitary gland, this in turn may well be secondary to a disturbance of the central nervous system (Harris, 1950). Other disturbances of the adrenal itself, and of other organs, may occur as primary features of this disease but there is as yet no certain evidence of them.

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pituitary gland. Thus in animals and man cortisone and hydrocortisone inhibit the secretion of ACTH and cause atrophy of the adrenal cortex when given in large doses (Sayers, 1950, Sprague and others, 1950; Ingle and Baker, 1953) and the chronic regulation of ACTH secretion (as distinct from acute responses to trauma, cold and emotional disturbances (Colfer and others, 1950, Fortier, 1951; Harris, 1950) seems largely dependent upon this mechanism. The co-existence of a high concentration of hydrocortisone in the plasma, and of an increased secretion rate of

adrenal cortex in this disease, must therefore involve some derangement of this regulating mechanism, whatever else is concerned with its etiology. In this connection it is interesting that in the last two trimesters of normal pregnancy the concentration of hydrocortisone in the plasma and the urinary excretion of its metabolites both rise steadily, so that in the last month these parameters reach values characteristic of Cushing's syndrome (Venning, 1946; Tobian, 1949; De Courcy and others, 1953; Bush, 1953a; Morris and Williams, 1953; Bayliss and others, 1955). These findings give a direct explanation of the many signs of Cushing's syndrome that have been found in isolation or together in normal pregnant women; and the occasional remissions of *rheumatoid arthritis*, noted by Hench, suggest that a disturbance in the regulation of the secretion of ACTH occurs in pregnancy similar to that in Cushing's syndrome, although milder in degree and of shorter duration. Cushing himself pointed out that the disease began very commonly in pregnancy or lactation in women, and Cohen (1937) described a remarkable case in which the disease appeared during a period of hyperemesis gravidarum, remitted after a spontaneous abortion and then recurred during the next pregnancy in conjunction with hyperemesis, and remitted following a second spontaneous abortion.

At present the known hormonal disturbances of this disease do not explain the occurrence of hypertension. From the results of Sprague and others (1950) with cortisone, this type of hormone seems unlikely to account for a rise of blood pressure of the order found. In adrenalectomized rats given salt in their diet or drinking water, dioxycortone and cortisone each produce a rise in pressure, and the administration of the two together produces a greater rise of pressure than either alone (Ledingham, 1954). It remains to be seen whether aldosterone in large doses, alone or in conjunction with other adrenocortical hormones, causes hypertension in man. If such an effect could not be demonstrated (bearing in mind the chronic nature of Cushing's syndrome) then it would be necessary to search for additional adrenal hormones or for extra-adrenal causes of the hypertension of this disease. In this connection, the findings of Wilkins and others (1952) are of great interest. These authors observed that the hypertension which was present in their cases of congenital bilateral adrenal hyperplasia was relieved by cortisone treatment; the disappearance of the hypertension followed closely the decrease in excretion of 17-ketosteroids, the latter being an index of successful inhibition of the adrenals of these patients by the action of cortisone on the anterior pituitary gland. These observations suggest very strongly that the adrenal cortex, at any rate in disease, can secrete a hormone having a hypertensive action in man and that this hormone is not cortisone (or hydrocortisone) itself.

DIAGNOSIS

From other Conditions. In its complete form, which is usual, Cushing's syndrome is not difficult to distinguish from other conditions. Nevertheless, simulating conditions occur. The adrenogenital syndrome or adrenal virilism, due to a tumour of the adrenal, or of the ovary, produces hirsuties of the same distribution as in Cushing's syndrome, but is usually associated with conspicuous enlargement of the clitoris in the female and of the penis in the male. In children, sexual precocity and an increase in bone age with premature ossification of the epiphyses is the rule. Striae, hypertension, osteoporosis and spontaneous fractures are usually absent. The urinary excretion of 17-ketosteroids is always increased, often greatly. Diabetes may occur in the so-called Achard-Thiers syndrome, a condition that resembles Cushing's syndrome and whose exact position seems rather uncertain.

Hypertension and obesity are common conditions in the female past middle age, minor degrees of hirsuties are not uncommon, and diabetes is by no means rare. Thus, some of the striking components of the syndrome may co-exist, as it were, fortuitously. Until the hormonal basis of Cushing's syndrome is accurately defined, and until it becomes possible easily to assay the substance in blood or urine, or both, such cases will continue to offer difficulty. If the obesity is of recent onset and the right distribution, if it is accompanied by moon-

... then Cushing's syndrome is clearly the probable answer. If the patient has a general obesity of long duration has a moderate hypertension

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... the next step is to try and locate the underlying lesion. Rare causes, such as a thymus tumour, should be sought by careful radiological examination. But in most instances the problem resolves itself into whether the patient has an adrenal tumour, and, if so, on which side. The tumour, if it exists, is occasionally big enough to be felt or to displace the kidney sufficiently to reveal a difference on palpation. More often, the tumour is revealed by radiological examination, either as a soft tissue mass above the kidney, or by displacement and distortion of the upper pole of the kidney outlined by intravenous pyelography. Finally, perirenal air insufflation (preferably by the presacral route, Blackwood, 1951) should be carried out and an intravenous pyelogram repeated. It is

to be noted, however, that radiological examination is not so revealing, as one might suppose and hope, in this condition, because the patients are so fat. The adrenal tumour that would seem to be the cause of the shadow in the radiogram has a tiresome way of having disappeared by the time it is exposed by the surgeon. Conversely, the failure to demonstrate an adrenal tumour does not mean none is present. The rapid development of a severe Cushing's syndrome with evidence of an adrenal tumour, particularly one that is growing quickly, should suggest to the physician the possibility of malignancy, a possibility that can only be confirmed or rejected at operation, unless metastases have already occurred. In the commonest type of case there is no adrenal tumour, but both adrenals tend to be enlarged; not, however, to the extent that this enlargement can be demonstrated radiologically. If a basophil adenoma of the pituitary exists, it is too small to produce clinical or radiological signs of its presence.

Fortunately, the dilemma is of comparatively little importance nowadays, when excision of all of one, and nine-tenths of the other, adrenal is the treatment of choice for cases without a tumour. Thus diagnosis is finally and correctly made at operation. The apparent demonstration of an adrenal tumour on one side merely suggests that that side should be exposed first; if a tumour is found it is removed and operation on the other side is not required.

TREATMENT AND ITS RESULTS

Irradiation of the Pituitary. Because of Cushing's suggestion that the underlying lesion was a small basophil adenoma of the pituitary, and because a pituitary lesion was supported by Crooke's histological studies, treatment was for many years largely directed to this gland. Roentgen irradiation of the gland, and the implantation of radon seeds into the sella turcica were the most effective remedies, but their effects were irregular and this form of treatment has now been abandoned.

Adrenalectomy. If an adrenal tumour is suspected and found, its removal usually produces a gradual return of the patient's condition towards normal. Unfortunately, some of these tumours are malignant and thus complete excision may be impossible; or an apparent complete removal may be followed after weeks, months or years, by metastases in lungs and elsewhere. In such cases the excision of the primary tumour is followed by great improvement in the manifestations of the hormonal disturbance with relapse as the metastases grow. Roentgen treatment of the site of the primary tumour or of the metastases is not particularly effective.

By far the most effective therapy in Cushing's syndrome, not due to a removable discrete tumour, is total or subtotal resection of the

adrenal glands (Priestley and others, 1951 and Sprague, Kvale and Priestley, 1953). Before cortisone was available this was an unsatisfactory treatment because, either too little adrenal was removed to produce improvement, or so much that the resulting adrenal insufficiency was difficult to control by DCA and crude extracts of the glands. The procedure which the above authors recommend and which is followed by my colleague Professor Rob and myself, is as follows. If an adrenal tumour is suspected, that gland is exposed first and the tumour, if found, is removed. If no tumour is suspected, or none found, then a bilateral operation using lumbar incisions is planned. If an atrophic gland is found, a piece is taken for section, but the rest is left *in situ*, the other adrenal is then explored with the expectation of finding a tumour, to be removed. If a normal or hyperplastic gland is encountered, nine-tenths of it is removed, the other adrenal is then explored and totally removed. Since the object of operation is to change the patient's state from one of excess, to one of deficient adrenal secretion, it is essential to provide adequate substitution therapy. Cortisone acetate, 200 mg. daily, is given on each of the two days before operation and on the day of operation, 100 mg is given on each of the first two days after operation and 50 mg. on the next two. A litre of isotonic NaCl solution is given intravenously on each of the first four post-operative days. The dose of cortisone is then adjusted to the individual, if no signs of deficiency occur, the dose is reduced to 25 mg for each of the next seven days, then reduced to 12.5 mg. per day for seven days and subsequently stopped, if possible. Some workers (e.g. Bishop and others, 1954) have found that nearly all patients so treated need doses of the order of 50 mg cortisone daily to prevent adrenal insufficiency, while others (e.g. Sprague and others, 1953, Beck and others, 1954) find no replacement therapy necessary in a substantial proportion of the cases.

One other practical point deserves emphasis: It has been known since Cushing's original paper that these patients are unusually susceptible to infection. It is, therefore, of great importance to prevent them from being exposed to infection, and to treat any infection acquired vigorously with antibiotics.

The most comprehensive results of adrenalectomy are those of Sprague, Kvale and Priestley (1953) who have described the results of 50 cases of Cushing's syndrome, treated by bilateral subtotal adrenalectomy. In 37 out of 39 patients, the weight of adrenal tissue removed exceeded 60 g. Of the 50 patients, six died in the immediate post-operative period, five of them at a time before cortisone was available, only one death out of 29 cases occurring with the substitution regime described above. Three other patients died after leaving hospital, one of adrenal insufficiency, one of suicide while mentally

depressed and one of hypertensive and coronary heart disease. Of the 41 surviving patients, 40 went into a complete or partial remission, although four had third operations to remove further adrenal tissue, and one had pituitary irradiation for a fulminating relapse eleven months after adrenalectomy. The duration of the post-operative period of observation in these 41 cases was three months to seven years. The proportion of remissions can be expected to diminish with time, since one recurred after a remission lasting four years. Twenty of their 41 patients were receiving substitution therapy of cortisone alone or cortisone plus desoxycorticosterone. In nearly all cases in which complete remission eventually occurred, a reaction began ten to twenty days after withdrawing adrenal cortical extract or cortisone. This reaction was characterized by weakness, depression, anorexia, nausea, vomiting, abdominal pain, fever, tachycardia and joint pains. "As a rule the blood pressure did not fall to the low levels commonly observed in acute adrenal insufficiency, and in some cases it remained elevated. The plasma electrolytes in some cases remained normal and in others showed changes characteristic of adrenal insufficiency." During this reaction, the excretion of 17-ketosteroids was absent or greatly reduced. This syndrome is promptly relieved by 100 mg. cortisone for a few days.

Effect of Bilateral Adrenalectomy on Blood Pressure. The blood pressure was significantly reduced in most, but not all, cases. Of the 44 patients who had some hypertension (over 150 mm. systolic or 90 mm. diastolic), 28 had normal and 16 elevated blood pressures after operation. Thirteen of the 16 patients with elevated blood pressures were well enough to leave hospital and "in all 13 there was a remission, or beginning remission, of all the other signs and symptoms of Cushing's syndrome. . . . In these cases, therefore, it is presumed that the hypertension was independent of adrenal cortical hyperfunction in its inception or that the patient was left with irreversible vascular disease attributable to the previous adrenal cortical hyperfunction, or both."

The results obtained by others have in general been similar. Bishop and others (1954) described six cases of whom five females responded satisfactorily. The only male had extensive renal damage and died "as an indirect result of hypertension, which did not respond to the adrenalectomy." Beck and others (1954) noted reduction in blood pressure to normal limits in four patients, one with severe malignant hypertension, one patient had a moderate reduction but died of cardiac failure, four months after operation; in one with malignant hypertension "neither blood pressure nor retinopathy has altered significantly in three post-operative weeks." Our own experience is similar. The blood pressure often returns to about the norm, but it may remain relatively unchanged in patients whose other signs have improved. Until the hormonal basis of the hypertension has been

elucidated, it will not be possible to say to what extent the residual hypertension is due to residual hormonal abnormality.

Effect of operation on other changes. As indicated, the effects of bilateral adrenalectomy on most of the other changes are striking. The face recovers its normal contours and becomes less red; the body shape returns to normal and weight is lost (Fig. 21.1b). The abnormal hair falls out. The hair of the scalp tends to become lighter, less greasy and ceases to fall out. Menstruation begins again and libido returns. Strength and energy return and the tendency to depression diminishes. Osteoporosis, however, tends to remain unchanged, for many months at least.

Treatment of the Hypertension. When hypertension is mild or moderate, it needs no treatment, and may be expected to improve after adrenalectomy in most cases. Should the arterial pressure be very high and signs suggestive of the onset of the malignant phase be present, such as ill-defined exudates or papilloedema in the fundus oculi or hæmaturia or impaired renal function, then treatment with methonium drugs should be begun at once, as described in Chapter 15, and maintained relentlessly until adrenalectomy. In some, no further treatment is required, but in those patients whose arterial pressure remains high after adrenalectomy, treatment is indicated and should be carried out as for essential hypertension as suggested in Chapter 15.

SUMMARY

High blood pressure is one of the more constant manifestations of Cushing's syndrome, the other features being obesity of face, neck and trunk, a high colour of the skin, atrophy of the skin with purple striae, amenorrhœa or impotence, hirsuties, acne, weakness, susceptibility to infection, diabetes and osteoporosis with spontaneous fractures. This syndrome is the result of an abnormal pattern of adrenal secretion, but the hormonal disturbance has not yet been accurately defined.

Removal of an adrenal tumour or bilateral subtotal adrenalectomy usually abolishes these disturbances, but in some cases hypertension persists. Until the hormonal disturbance can be defined and measured, it is not possible to say whether or not the residual hypertension is due to a residual hormonal abnormality, or is another example of persistence of raised pressure when the original causative lesion has been removed.

In Cushing's syndrome the hypertension may be in the benign or malignant phase. In some instances adrenalectomy reduces arterial pressure and abolishes the manifestations of the malignant phase.

CHAPTER 22

COARCTATION OF THE AORTA

COARCTATION of the aorta is a congenital abnormality, in which the aorta is greatly narrowed or completely occluded. The occlusion is usually situated at about the point where the Ductus Arteriosus joins it, and just distal to the origin of the left subclavian artery ; but it may be just proximal to that vessel, and, very occasionally, the narrowing is just above the diaphragm or, indeed, in the abdominal aorta just above the renal arteries (Kondo and others, 1950). As a rule, the arterial pressure (systolic, diastolic and mean) is high in the area above the constriction, while the pressure, systolic, diastolic and mean, may be high, normal or low distally, the pulse pressure is usually greater than normal proximal, and less than normal distal, to the coarctation.

It is usual to divide coarctation of the aorta into two types, the infantile and the adult. The infantile type comprises a group in which there is a long segment of constriction usually involving the distal third, or half of the aortic arch, often associated with severe intracardiac abnormality, leading to death in the first year of life. In the adult type, the block involves only a short segment, other malformations are less common and the patient may survive to old age (maximum = 92 years, White, 1944). As Gross (1950) has pointed out, there is so much overlapping between groups as to make the classification arbitrary and, in an age of surgical repair, useless.

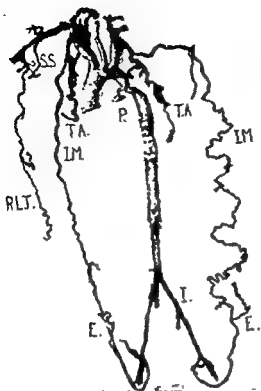
In coarctation of the aorta, the blood to the lower part of the body is delivered through enlarged collateral arteries connecting the main branches which join the aorta above and below the constriction. These anastomoses are :

(1) By the scapular and cervical branches of the subclavian and axillary arteries, to the lateral and dorsal branches of the aortic intercostals, forming a network around the scapula and in the neck.

(2) By the musculo-phrenic branch of the internal mammary to the inferior phrenic branches of the abdominal aorta, and the smaller superior phrenic branches of the thoracic aorta, forming a network above and below the diaphragm

(3) By the upper two intercostals, arising from the superior intercostal branch of the subclavian, to the upper aortic intercostals (Bramwell and Jones, 1941).

This anastomotic supply is shown in Fig. 22.1.



FIG

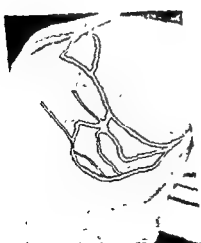


FIG 22 2 Pulsating arteries mapped and photographed in two cases of coarctation of the aorta. (Lewis, *Heart*, 1933, 16, 205)

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CLINICAL COURSE IN COARCTATION OF THE AORTA

Reifenstein, Levine and Gross (1947) and Gross (1950) reviewed 104 published cases verified *post mortem*. The ratio of males to females was five to one. The age at death was three to 76 years, average age 35; 61 per cent. died before they had completed their 40th year. The mode of death was of five kinds: (1) about 26 per cent. lived far into adult life, often into old age, with little or no incapacity. In this group death was most common in the fifth decade, the average age being 47 years, and was due to incidental causes, such as carcinoma, sepsis and coronary thrombosis. (2) About one-fourth (22 per cent.) died from bacterial endocarditis infecting either an associated congenital or rheumatic lesion of the valves, particularly bicuspid aortic valves, or of the aorta just distal to, or proximal to, the area of constriction, or, more usually, a combination of these places. Deaths were most common in the third decade, the average age at death being 28 years. The symptoms and course were those commonly found in bacterial endocarditis, aortic regurgitation being a frequent development in those with involvement of the aortic valves. (3) About one-fourth (23 per cent.) died suddenly from rupture of the aorta, either the ascending aorta (18 per cent., average age 30.0 years) or the descending aorta just distal to the constriction (5 per cent., average age 19 years). Patients who died from rupture of the ascending aorta had the usual symptoms of dissecting aneurysm, death being most commonly due to hæmo-pericardium. Distal ruptures entered the bronchus, œsophagus and pleural cavity. Death was usually sudden. (4) Eighteen per cent. died from congestive cardiac failure, nearly always in association with other cardiac lesions. Thus of 18 patients, 12 had chronic valvular disease, three had chronic valvular disease and coronary artery disease, three other patients had other heart disease, and in only one were no associated cardiac abnormalities found. Hypertension was present in all but one. Deaths from cardiac failure were commonest in the fourth and fifth decades, the average age at death being 39 years. (5) In 11 per cent. death occurred from intracranial hæmorrhage, between the ages of 11 and 51, average age 28.0 years. The brain was examined in six cases.

... were of the usual congenital type involving the circle of Willis and its main branches.

Coarctation of the aorta, located in its usual position, is the only form of hypertension in which I have never seen the malignant phase develop. Nor am I acquainted with a published case. Granström (1951), who examined the eyes in 40 cases referred to Crafoord for

CLINICAL COURSE IN COARCTATION OF THE AORTA

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operation, found that corkscrew arteries were the rule, but that real irregularities in calibre were usually absent. He never saw papilloedema or exudates. Fisher and Corcoran (1952) described a boy aged 14 with a pressure of 238/160 in his right arm, and papilloedema, who had a congenital narrowing of the aorta at the origin of both renal arteries. The kidneys were normal histologically but fibrinoid change was found in the adventitia of the aorta. Goldzieher and others (1951) described a woman of 45 with paroxysms of hypertension resembling phæochromocytoma with an aortic narrowing in the same place. One other anatomical peculiarity is worth noting. Graybiel, Allen and White (1935) measured the wall/lumen ratio of small arteries obtained by biopsy from muscle and skin of upper and lower limbs of five cases of coarctation, aged 20 to 33 years, and were unable to detect any muscular hypertrophy, splitting of the elastic lamina or hyaline or fatty degeneration. In the absence of evidence of muscular hypertrophy of small arteries, the hypertension in the upper part of the body in coarctation contrasts also with acquired hypertension in all its forms.

THE DIAGNOSIS OF COARCTATION OF THE AORTA

There is nothing very characteristic in the symptomatology of coarctation of the aorta. The patient may present for the first time with symptoms of bacterial endocarditis, rupture of the aorta or intracranial hæmorrhage; and the presence of high arterial pressure in a patient with those conditions should prompt a search for the characteristic signs. The complaints may be those of heart disease, especially breathlessness and palpitations, or of effort syndrome (neurocirculatory asthenia, cardiac neurosis), especially left inframammary pain, palpitations and giddiness, or there may be weakness in the legs. Quite often, the condition is discovered by chance during physical examination, the forceful beating of the neck arteries, the hypertension, or the murmurs on the front or back of the chest, being noted by the doctor.

By far the most constant and useful sign of coarctation of the aorta, at least of the common type, is the contrast between the forceful and rather abrupt pulsation of the arteries in the neck, the wrist and the episternal notch, and the feeble slow rising femoral pulses at the groin (Lewis, 1933). Abbott (1928) considered that an elevated arterial pressure in the arms associated with no recordable, or a lowered, blood pressure in the legs was the most important sign of coarctation. While this is, in general, true, determination of blood pressure in the legs takes a great deal more time than a comparison of the pulses at wrist and groin, which is so simple that it should be part of the routine examination of all patients with hypertension. As Lewis (1933) pointed out, not only is the femoral pulse small, its summit is delayed as compared with that of the radial; this point, too, can be ascertained by palpation.

The pulses at the ankle are similarly reduced. The next important sign, and that which is diagnostic, is the demonstration of grossly enlarged collateral arteries joining the greatly enlarged transverse cervical, transverse scapular and internal mammary arteries, which leave the aorta above the coarctation and anastomose with the intercostal and other arteries entering the aorta below the coarctation. These enlarged collateral channels can be seen and felt under the skin between and below the shoulder blades (Fig. 22-2). These arteries can be most easily seen if the patient stands and then bends so that his hands rest on his knees, the now horizontal back being viewed with a

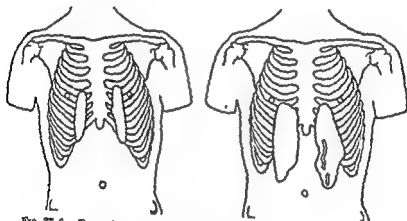


FIG. 22-3 Shows distribution of systolic murmurs in two cases of coarctation of aorta (Lewis, *Heart*, 1933, 16, 205.)

good light passing nearly horizontally across it. The arterial pressure in the upper limbs is raised, the systolic more than the diastolic, presumably because a normal systolic output from the left ventricle has to be accommodated in the small aortic segment above the constriction. The systolic pressure is always, and the diastolic pressure is often, lower in the legs than in the arms. If the constriction lies proximal to the femoral artery, the pressure in the left arm is lower than in the right arm. If the constriction lies distal to the femoral artery, the pressure in the left arm is higher than in the right arm. The signs being those of enlargement of the left ventricle. A rather late systolic murmur is common, and as Lewis (1933) pointed out, has a rather characteristic distribution on either side of the lower sternum over the internal mammary arteries (Fig. 22-3); a similar murmur is often heard over the enlarged collateral channels in the back, particularly between the scapulae. Other congenital cardiac lesions may modify the signs. Thus a subaortic stenosis will reduce the arterial pulsation in the upper extremities, while a patent ductus arteriosus may give signs of right ventricular enlargement, systolic movement of the

the fourth and fifth costal cartilages, as well as its own characteristic murmur.

Radiologically, the characteristic sign is the scalloping or notching of the lower borders of the ribs, produced by the enlarged and tortuous intercostal arteries. These erosions are multiple, bilateral and limited to the lower borders of the posterior parts of the ribs. They are visible from about the age of six years onwards. The antero-posterior silhouette of the heart has no constant characteristics; the aortic arch may be small, normal or large. The characteristic findings are seen in the oblique views where the aortic arch cannot be traced out. The aorta and its unusually prominent branches rise as a conspicuous column from the heart high into the thorax and root of the neck. Behind this column there is an area of abnormal clearness opposite the bodies of the sixth and seventh and eighth dorsal vertebrae. Proof of the existence of coarctation and its exact location and delimitation can be obtained by passing a polythene catheter into the aorta through a carotid or temporal artery and injecting into it diiodone, when the aorta and its collateral vessels may be visualized (Freeman and others, 1950).

SURGICAL REPAIR OF COARCTATION

Although Blalock had suggested, as a result of experiments in dogs, that surgical repair of aortic coarctation was feasible in man, the first reconstructions were performed by Crafoord (Crafoord and Nylin, 1945) and Gross (1945) in 1944 and 1945. They showed that the stenotic segment of the aorta could be successfully excised, the proximal and distal ends being sutured together. This operation has now become standard practice in units for thoracic surgery. The two chief technical difficulties, namely, a long stenosed segment and degenerative changes in the aorta, can frequently be surmounted by the use of preserved aortic homografts, and even the insertion of a nylon sleeve. Before the use of homografts, it was generally accepted that the ideal age for operation was between five and 15 years, beyond 15 sclerotic changes in the aorta are increasingly frequent and make simple resuture correspondingly difficult. As has been noted, homografts have overcome to some extent this technical difficulty. But, in view of the prognosis, it is still desirable to repair the lesion at as young an age as practicable. Bing and others (1948) reported 22 patients in whom surgical repair had been attempted and accomplished in 21. In 17 the stenosis was resected and the proximal and distal ends of aorta joined together; in four the proximal end could not be mobilized sufficiently and the left subclavian was joined to the distal end of the aorta. There were three immediate deaths. The arterial pressure averaged 183/106 in the arms and 91/68 in the legs, before operation,

and 141/85 in the arms and 128/78 in the legs, after operation. Improvements in anaesthesia, antibiotics and the availability of homografts have probably reduced mortality below 10 per cent. in most clinics, and it is very generally agreed that since about 60 per cent. of patients with coarctation die before 40, surgical repair is justifiable in all

MEAN PRESSURES

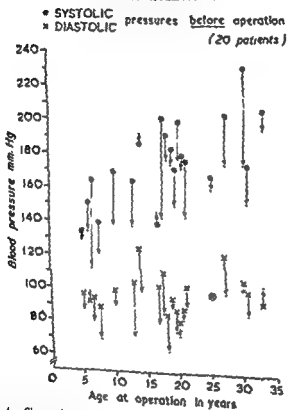


FIG 22.4 Shows the average values for systolic and diastolic pressures before and after repair; point of the average readings obtained (unpublished)

patients—

It is rather common for patients who have had surgical repair of coarctation of the aorta to have a residual narrowing of the aorta. This is usually detected by a follow-up examination of the chest X-ray, which shows a narrowing of the aorta at the site of the repair. In some cases, the narrowing is mild and does not require further treatment. In other cases, the narrowing is severe and may require a second surgical repair. It is important to monitor patients who have had surgical repair of coarctation of the aorta for residual narrowing of the aorta.

of the aortic constriction and end to end anastomosis, except in one case where an aortic graft was inserted. I am grateful to them for allowing me the use of their data and figures before publication. Observations were made for periods from three to 60 months after operation. The blood pressure showed considerable fluctuation before and after operation. But while there was considerable overlap, the blood pressure after operation tended to be lower than before. Fig. 22.4 shows the means of the readings made in the upper limbs before

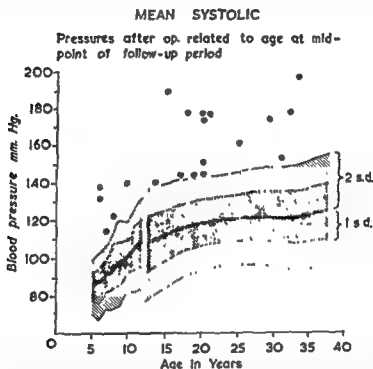


FIG. 22.5. The average values for systolic pressure after repair of aortic coarctation related to the values found in a sample of the general population. Readings of arterial pressure obtained in the first month after operation have been excluded. (Cleveland, Counihan and Goodwin (unpublished).)

and after operation, excluding values obtained in the first month after operation. A comparison of the mean postoperative blood pressures with those found in the general population (using the data of Stocks (1924) and Hamilton and others (1954a)) is shown in Figs. 22.5 and 22.6. The systolic pressures are all above the upper normal range; those for diastolic are mostly in the upper range or above it. Thus the pressure after repair remains unusually high. They concluded that the residual hypertension was not due to narrowing of the aorta at the site of anastomosis, since the diameters of the rejoined aorta were satisfactory at operation, since all clinical evidence for enlarged

MEAN DIASTOLIC

Pressures after op. related to age at mid-point of follow-up period.

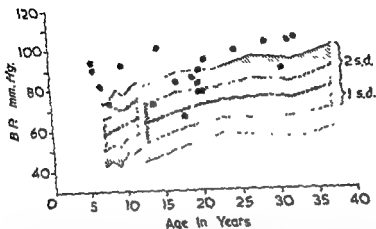


FIG 23 G. The average values for diastolic pressure after repair of aortic coarctation related to the values found in a sample of the general population. Readings of arterial pressure obtained in the first month after operation have been excluded (Cleland, Counihan and Goodwin (unpublished)).

collateral vessels disappeared, and since no delay could be detected in the femoral pulse after operation.

THE MECHANISM OF HYPERTENSION IN COARCTATION OF THE AORTA

The frequency with which elevation of the arterial pressure is found in the arms in coarctation of the aorta was stressed by Lewis (1933). Since the systolic pressure was always much lower in the legs it was generally assumed that the arterial pressure below the constriction was normal or low. However, Steele (1941) showed that this was not necessarily true. In practically all of 217 cases collected by King (1937) and himself, the systolic pressure was above 140 mm. Hg. and in about one-half the diastolic was over 100 mm. Hg in at least one arm. The arterial pressure had been measured in the legs in 65 cases; the most striking feature was the low pulse pressure, but a diastolic of over 100 had been recorded in 12. Steele recorded simultaneously pressures from radial and femoral arteries in three cases of coarctation. The most striking difference was in the pulse pressure, which was increased in the arms and decreased in the legs. He therefore suggested that there was vasoconstriction in the lower as well as the upper part of the body, and suggested that this might be renal in origin.

There have thus been two rival hypotheses to explain hypertension in coarctation of the aorta. The obvious and simple explanation is that elevated arterial pressure in the upper part of the body is due to the increased resistance offered by the collateral vessels transmitting blood to the lower part of the body. Lewis (1933) examined this possibility and rejected it on the grounds that the sum of the cross-sectional areas of innominate, left carotid, left subclavian and isthmus was approximately equal to the cross-sectional area of the aorta. However, resistance is an inverse function of the fourth power of the radius and also of the length of the vessel and, as Fig. 22, 1 clearly illustrates, the length of the vessels connecting the aorta proximal and distal to the constriction is very large.

An alternative explanation grew with the demonstration that hypertension could be produced by renal artery constriction. Goldblatt and Kahn (1938) showed that constriction of the aorta would produce hypertension if the clamp were placed proximal to the renal arteries in the dog, but not if placed distally. Ryland (1938) showed that constricting the aorta between the renal arteries would produce hypertension in the rat, and that the hypertension was abolished by removing the kidney distal to the obstruction. Sealy, de Maria and Harris (1950) succeeded in producing a rather closer experimental analogy to coarctation by inserting a narrowed lucite tube into the thoracic aorta of dogs. The arterial pressure immediately afterwards fell in the femoral, and then rose slowly over several months in both carotids and femorals, so that the arterial pressure above the constriction was raised considerably, while that below the constriction was raised slightly as compared with the initial values. Scott and Bahnson (1951) produced an artificial coarctation by establishing an end-to-end anastomosis between the left subclavian artery and the thoracic aorta, and then dividing the aorta above the anastomosis. Systolic and diastolic pressures rose steadily for about six weeks in the carotid and then remained stable; femoral pressure fell in the first few days and then rose so that after about four weeks femoral pressure also exceeded the initial value. In such animals, transplantation of a kidney to the neck, followed by removal of the other kidney restored the carotid pressure quickly to its initial level.

Observations on man are far from conclusive in establishing either hypothesis. The cardiac output seems to be within the normal, or

1948). Lewis (1933) found the blood flow through the brachial, and the calf and foot essentially normal in coarctation. Bing and others (1948) found that in comparison with post-operative values, the pre-operative figures for forearm blood flow were high, and for calf blood-

flow, low. Prinzmetal and Wilson (1936) found that the increase in forearm blood flow produced by raising body temperature, was greater in subjects with coarctation of the aorta than in normal subjects, or in subjects with essential hypertension. They regarded this as evidence for the vasomotor nervous origin of hypertension in coarctation. However, in the hand the rate of blood flow after removing vasomotor nervous tone was the same in subjects with coarctation as in normal subjects, or those with essential hypertension (Pickering, 1936b). Believing at that time that the hypertension was restricted to the upper part of the body, I attributed this effect to lessened growth (diameter) of the blood vessels of the upper limb—the obverse, in fact, of the increased growth of the collateral vessels joining proximal and distal segments of aorta. Alternatively, the upper limb arteries and arterioles may have grown longer. These observations have, unfortunately, never been repeated on patients before and after surgical repair.

In view of the hypothesis that the hypertension is due to renal ischaemia great interest has been shown in the renal circulation in coarctation of the aorta. The first observations were those of Friedman and others (1941) who found, in six cases, a normal glomerular filtration rate and a moderate increase in renal plasma flow.

Subsequently, the filtration rate increased in five, was unchanged in five and decreased in two; renal plasma flow increased in seven, remained unchanged in four and decreased in two.

However, this team (Bing and others, 1948) did not believe renal ischaemia was the cause of hypertension. They calculated that the overall resistance, exclusive of the coarctation and collaterals, was below normal, and they thought it, moreover, unequal, being higher above than below the constriction. They therefore concluded that it could not be of renal origin. Harris and others (1950) came to a similar conclusion. In four cases they found that glomerular filtration rate and plasma flow were both decreased before operation. Seven to 11 days after repair, glomerular filtration rate and renal blood flow had increased almost to normal values. After 60 to 112 days, the brachial arterial pressure had fallen further but the renal circulation had returned to its pre-operative values.

More recently, by Gómez's (1951) the peripheral resistance was increased and the afferent

decreased ; in two patients the renal plasma flow was decreased, and the filtration fraction increased, the increased resistance being in the efferent and venular segments. Repair of coarctation tended to restore renal circulation to normal. The authors believed these renal circulatory changes were not the cause of the hypertension, but were a consequence of the aortic obstruction.

Culbertson and others (1954) have studied the renal circulation in 14 patients, 10 of whom had their cardiac output measured, and eight their hepatic blood flow. Seven had elevated cardiac outputs, one a normal output and two, with cardiac failure, low values. Renal plasma flow was elevated in one, normal in eight and subnormal in five (of whom three were in heart failure). Hepatic blood flow was decreased in three and normal in five. They concluded that their data did not show significantly increased arteriolar resistance locally or generally, diastolic hypertension or renal ischaemia in patients not in cardiac failure.

In prospect, it seemed that elevated arterial pressure, due to a clearly defined anatomical lesion such as a congenital narrowing of the isthmus of the aorta, would prove to have a simple and easily definable explanation. Such, however, has not proved to be the case. Even when the essential abnormality is repaired, the arterial pressure remains relatively high. Once again we have an example of the thesis so often presented here, namely, that removal of what appears to be the exciting cause does not necessarily restore arterial pressure to the norm for that age. This example above all others, suggests that our narrow world of concepts, bounded by thickening of intima, media or adventia on the one hand, and by nervous and humoral vasoconstriction on the other, is too confined. The abnormality in coarctation would seem to be none of these. As an alternative there is the suggestion that the vessels in the upper part of the body have grown differently. They may be inherently smaller or longer. Some doubt may be entertained as to whether such an explanation is in any case sufficient ; for when the continuity of the aorta is restored, so that blood is supplied by the normal route to the lower part of the body, the arterial pressure in the upper limbs remains higher than expected, though it is less than it was before operation. Perhaps some part of the mechanism for regulating blood pressure has got adjusted to a level higher than normal. What is of great interest is that when the vascular territories of the lower part of the body are reopened by repair of the aorta, the pressure stays up. This makes it unlikely that abnormal vascular growth in the upper body is the only effective factor.

SUMMARY

Coarctation of the aorta is a congenital affection in which the aorta is narrowed or obliterated, usually near the origin of the ductus

arteriosus, and in which the arterial pressure is raised above, and, in some cases, below, the constriction. The mechanism by which the arterial pressure is raised is not known. Repair of the coarctation reduces the arterial pressure, but leaves it above the norm for that age. This seems to be another instance in which removal of the abnormality, originally responsible for the hypertension, fails to restore the arterial pressure to the expected norm.

CHAPTER 23

HYPERTENSION AND PREGNANCY

In studying the problem of pregnancy and hypertension we become painfully aware of the ills of specialism. For, since all to do with the pregnant woman has been so long the province of the obstetrician, a mere physician seeking to make himself familiar with the facts is confronted at once with a new set of concepts and a new technical jargon with which he must first become familiar. Happily, most of these exotic concepts, as it were the hot-house plants of specialism, such as the "low reserve kidney" and "occult nephritis," are on the way out and their demise needs no speeding from my pen. One of these peculiar names, however, survives though its usage has been somewhat altered. The "toxæmias of pregnancy" originally implied a group of diseases thought to be peculiar to pregnancy, and ascribed to the effect of poisons liberated into the blood stream from the pregnant uterus, though there were other claimants for this doubtful privilege, and the Dublin School believed the gut was the source of the toxins. It is now known that many of those diverse conditions are not peculiar to pregnancy and are, in fact, deficiency diseases, which are brought on by pregnancy either because of the demands of the fœtus or because of anorexia and vomiting, examples being Wernicke's encephalopathy, probably a vitamin B complex deficiency, and hyperemesis gravidarum, often terminating in an acute hepatic necrosis, due to deficiency of sulphur containing amino-acids. Nowadays pregnancy toxæmia¹ means no more or less than a specific hypertensive disease of pregnancy, that will be a main topic of this chapter. Although the toxin in the blood remains to be demonstrated, the idea that the condition is humoral is as likely as any other and the name may be allowed to stand.

¹ Although this would seem to be common usage many text-books still use the term *toxæmia of pregnancy* and have the misfortune to say that it is "not a disease" and "not a condition."

(3) Pre-eclampsia.

(4) Eclampsia.

past, or utter confusion of mind. I am tempted to urge that the term *toxæmia of pregnancy* remains so meaningless that it had better be abolished completely and finally. To echo Herrick (quoted by Welfen, 1940): "Such a loosely used and inclusive term as *toxæmia of pregnancy* can no longer be accepted as precise or specific. It should be subjected to critical analysis, perhaps dissected until there is nothing left."

The association between pregnancy and high blood pressure may

say, the hypertension was present before the pregnancy or is due to a malady that has no direct connection with pregnancy. These two must be carefully distinguished and will be separately treated. Some idea of the distribution of different types of hypertension may be obtained from Table 23.1. Browne (1947) adopts 120/80 as the

TABLE 23.1 *Distribution of different Types of Hypertension in Pregnancy.*

University College Hospital, London (Browne, 1947)		Bellevue Hospital, New York, 1936-50 (Wellen, 1953)	
	Per cent		Per cent.
Pre-eclamptic toxæmia	70	Specific hypertensive disease of pregnancy	72.1
Chronic hypertensive vascular disease	25	Essential hypertension	13.9
Chronic nephritis	5	Same with specific hyperten- sive disease of pregnancy	5.9
		Glomerulonephritis	1.6
		Unclassified	6.3

dividing line between normal and high pressure. Wellen (1953) gives no figure, but presumably takes 140/90, which is common obstetrical practice

I. THE NORMAL EFFECTS OF PREGNANCY

In normal women with pressure in the lower ranges, pregnancy has little or no effect on the arterial pressure; nor does protein appear in the urine. Dexter and Weiss (1941) found, however, that œdema occurred in 64 per cent of 100 otherwise normal women. This œdema was slight, did not pit on pressure and did not involve the serous cavities. It occurred in the last three months of pregnancy and usually disappeared rapidly after delivery. Without having made such careful observations I can confirm that about this proportion of pregnant women find they cannot get their wedding ring off the finger in the last stages of pregnancy.

II. SPECIFIC HYPERTENSIVE DISEASE OF PREGNANCY; PRE-ECLAMPTIC AND ECLAMPTIC TOXÆMIA

Specific hypertensive disease of pregnancy or pre-eclamptic toxæmia is characterized by the appearance of hypertension, œdema and proteinuria never before the twentieth and nearly always after the

twenty-fourth week of pregnancy. It is usual to regard 140/90 as the dividing line between normal and abnormal blood pressure, but Browne (1947) accepts Robinson and Brucer's figures of 120/80. It is a condition for the diagnosis of pre-eclamptic toxæmia that the readings of blood pressure taken before the twentieth week shall have been normal. If the arterial pressure is above either of these figures (according to the predilection of the author) before the twentieth week, the case becomes one of hypertension preceding or independent of pregnancy, and if proteinuria supervenes it becomes one of toxæmia complicating hypertension. The reader may suspect, as the author does, that much of what is subsequently described under these two headings forms a continuous and not a discontinuous series, the division between "hypertension" and "normal" being as artificial in those who bear young as in those who do not or have already done so. Yet we must persist with the nomenclature, because all facts are described in terms of it.

Clinical Features

The woman who develops pre-eclamptic toxæmia will have had an uneventful pregnancy until after usually the twenty-fourth week. At some subsequent time, routine examination discloses proteinuria or hypertension, or both, and a variable degree of œdema. Browne (1944) states that proteinuria never precedes hypertension. Dexter and Weiss (1941) found that in four of 49 patients, proteinuria preceded an increase in blood pressure, in 31 cases a rise of blood pressure preceded proteinuria and in 14 hypertension and proteinuria appeared simultaneously. From then on, these three manifestations, proteinuria, hypertension and œdema usually continue until pregnancy is terminated. Examination in the early stages reveals a moderate elevation of both systolic and diastolic pressures, proteinuria, which may vary from a trace to a heavy cloud on testing, and a slight generalized œdema. There are usually no other signs, renal function is normal to all tests except the diuretic response to a litre of water; the urinary deposit reveals no excess of red or white cells in the early stages, but an increase of both types of cell and of various casts may be found in some cases. If the patient is adequately supervised, and if, in particular, she receives enough rest, the situation may remain unchanged till term, or the pressure may fall and the proteinuria diminish. If treatment is inadequate, or, less commonly, in spite of treatment, the pressure may rise, proteinuria and œdema increase, and the following undesirable complications ensue:

(1) *Headache, nausea, vomiting and drowsiness* separately and, more especially, in combination suggest that the case is passing from the relatively mild pre-eclampsia to that of the more severe eclampsia.

(2) *Eclampsia* is characterized by *hypertensive fits*. The patient complains of headache and often nausea, becomes irritable or drowsy and then, after some strong sensory stimulus, or even in its absence, has a generalized epileptiform convulsion followed by coma. There may be a single fit, or the fits may be frequently repeated. Usually, the onset of a fit is preceded by an acute rise of arterial pressure. After many fits, the arterial pressure may fall, the skin becomes cold and clammy and the patient may die of peripheral circulatory failure.

The pathogenesis of these fits has been considered at length on page 260. They have, as we have seen, been attributed to cerebral arterial spasm or to acute cerebral oedema. The preceding rise of arterial pressure would fit either hypothesis. Those who like to attribute all obscure manifestations to vascular spasm naturally prefer this hypothesis; it has always seemed inherently unlikely to the writer, but Byrom's recent evidence from the rat makes it more plausible (see page 94). Against the idea is, however, the very ancient observation originally made by Baker in 1859, that the fits can be relieved by extracts of *veratrum viride* which reduce arterial pressure reflexly from receptors in the heart (see page 323). McCall (1953) has shown that the effect of this substance on cerebral vascular resistance in toxæmia of pregnancy is almost exactly balanced by its effect on arterial pressure, so that no change occurs in cerebral blood flow. Against the hypothesis of oedema of the brain is Sheehan's 1950 finding that oedema of the brain is only found in eclampsia if the necropsy is delayed two hours or more, long enough to allow autolysis, though he points out that exact estimates of water content of the brain have never been made.

Sheehan (1950), whose pathological investigations in this subject are unique, because of his insistence on examination early after death, gives the following account of cerebral lesions. In about one-third there are cerebral lesions visible to the naked eye, a single hæmorrhage, varying in size from small to massive, in pons, basal ganglia or cerebral white matter, or small areas of softening in the basal ganglia. There may be capillary hæmorrhages, the cerebral capillaries may contain colloid thrombi, and their walls may show fibrinoid or fatty change. Clearly, it would seem wise to reserve judgment as to the precise cause of the fits.

(3) *Cerebral hæmorrhage* is a not infrequent cause of death in eclampsia. As is usual in such cases it is difficult at necropsy to decide from which vessel the blood issued, let alone the nature of the vascular lesion.

(4) *Increase in Oedema*. Proteinuria may become so massive as to produce hypoproteinæmia with consequent increase in oedema. Unless salt and water intake are restricted, oedema may also become massive,

because of reduced output. Gross œdema may make labour difficult and adversely affect fits, heart failure and the retinal changes.

(5) *Suppression of Urine.* With increase in œdema the output of urine falls. In severe cases the urinary output may fall to a few millilitres or cease altogether. In these cases, it is usual to find *post mortem* either a bilateral cortical necrosis of the kidneys, or the changes described under acute tubular necrosis. In the latter case, hæm pigments and pigment casts are often found in the small volumes of urine secreted. These conditions may occur during or just after labour, or in abortion without preceding toxæmia, but sometimes complicate the latter.

(6) *Renal Failure.* In most cases of pre-eclampsia and eclampsia, the blood urea, and the ability of the kidney to concentrate urea are normal. Renal failure may occur as a result of three complications, bilateral cortical necrosis, acute tubular necrosis and a fulminating malignant hypertension with numerous acute necroses of glomeruli and arterioles. In the first two conditions the urine becomes very small in amount and may be, in composition, almost an ultrafiltrate of plasma. Since they are reversible, they should be treated as indicated on p. 342. Malignant hypertension is associated with neuro-retinopathy and high arterial pressure and demands the use of hypotensive drugs, such as the hexamethonium series.

(7) *Left Ventricular Failure.* The patient suddenly becomes breathless, and sits up in bed, pale, anxious, sweating, and the breathing fast, laboured, and shallow. The attack may end quickly, or may go on to the stage of acute pulmonary œdema, with the welling up of copious pink frothy sputum, and finally death in asphyxia.

(8) *Congestive Failure.* Failure of the congestive type is a less common complication.

(9) *Hypertensive Neuro-retinopathy.* In most women who develop eclampsia, and in some others with the more severe grades of hypertension, neuro-retinopathy develops. The neuro-retinopathy is of the usual type (p. 276), except that retinal œdema is more severe, and detachment of the retina is more apt to occur, differences that may perhaps be attributed to the massive œdema of all the tissues that is usually present. The neuro-retinopathy usually begins with the appearance of one or several large ill-defined exudates, soon followed by the appearance of more, and by well-defined papilloedema and œdema of the retina. It is in this condition that Myhus (1928) described contractions of the retinal arteries passing along them like peristaltic waves. Wagener (1933) agreed with Mylius, finding as the arterial pressure rose: (1) a narrowing of the retinal arteries affecting any or all branches; (2) irregular constrictions first or most marked on the nasal branches "which may vary in degree and situation from day

to day" Later as the narrowing and constrictions become more fixed, retinitis supervenes. I have also seen localized narrowings of the retinal arteries develop in toxæmia of pregnancy, in patients with the higher pressures, but those that I have been able to see have remained fixed, and therefore have the character of organic changes. Of my ophthalmological colleagues interested in this question, only Juler (1949) has been able to see localized narrowings that come and go, and these have been slight in degree.

The Malignant Phase of Hypertension

The syndrome of neuro-retinopathy with a tendency to hypertensive fits, suppression of urine and left ventricular failure, is a clinical picture which we have met before and is strongly suggestive of the malignant phase of hypertension. Sure enough, acute arteriolar necroses affecting kidneys, gut, adrenals, brain, eye and the other usually affected territories have been described in such cases by Klemperer and Otani (1931), Dexter and Weiss (1941) and by Heptinstall (1953). McKelvey and MacMahon (1935), however, state that, in patients who died during or immediately following a pregnancy followed by a non-convulsive toxæmia, and in whom no history of previous hypertension was obtained, the kidneys showed the changes of toxæmia, but in no case the characteristic lesion of malignant nephrosclerosis. In a second group, diagnosed as "nephritic toxæmia," in which hypertension had existed for two to seven years before pregnancy, the lesions of malignant hypertension were found in every case. Heptinstall's three cases all dying of uræmia within three months of delivery and all having arteriolar necroses in kidneys and the other usual organs, were aged 24, 41 and 37. The first patient was a primipara who was noticed to have severe hypertension at the eighth week. The second started her pregnancy with a normal blood pressure, and, although hypertensive at term, did not become severely so till two months later. The third had had a normal first delivery five years previously but had developed severe hypertension with her second child.

The syndrome occurs in those patients (a) who have suffered the largest rise of pressure in pregnancy, and (b) whose pressures have reached the highest levels. All the manifestations, fits, neuro-retinopathy, heart failure, and renal disturbances usually disappear if the arterial pressure falls.

agree

that

the malignant phase is a manifestation of the severity of the hypertension. There is, however, one new and striking fact to add. In the St. Erik's Hospital, Stockholm series, neuro-retinopathy occurred in patients with toxæmia of pregnancy whose arterial pressure averaged

facts are in general

this book (p. 290)

pressure fell to normal before delivery. They obtained rather similar figures for proteinuria and oedema and concluded, therefore, that the reversal of the phenomena of toxæmia after parturition was due to loss of the placenta and not to loss of the foetus; for, although, after foetal death, the foetus is retained, its circulation has ceased and it can scarcely be the source of a chemical substance that is being absorbed into the mother. In a very few cases in which there is no evidence for the onset of the malignant phase, the pressure may not fall after parturition, or the fall is very transient, lasting hours or days. In some such cases, hypertension was undoubtedly present before pregnancy. But there are some in whom it was not. It is clear that something has happened that has made the hypertension self-perpetuating. Here is another example of an oft-recurring theme in hypertension. It would be easy to cite this as another example of the vicious circle of Volhard (1931), where organic lesions in the renal arteries induce renal ischaemia that itself gives hypertension. This may indeed be the explanation. But the absence of any systematic observation to test the hypothesis, and the occurrence of the phenomenon under other circumstances where this explanation cannot hold (see p. 374), forbid any positive conclusion in the matter.

THE CONSEQUENCES TO THE MOTHER OF SPECIFIC HYPERTENSIVE DISEASE OF PREGNANCY

Immediate. The immediate consequences to the mother vary much with the stage at which the malady is first recognized; and the method of treatment adopted. Nowadays with rest, sedation and delivery before the arterial pressure has risen to high levels, the immediate mortality is small, provided the case is seen sufficiently early. At one time, eclampsia carried a mortality of over 50 per cent. Theobald (1950) records that he lost three cases out of 50 or 60 treated with morphine in a dimmed room; two of these cases developed hyperpyrexia. Chesley, Somers and Vann (1948), recording the whole experience of a maternity hospital in New Jersey from 1931 through 1945, recorded 245 cases of convulsions and three of non-convulsive eclampsia, an incidence of 0.3 per cent. of all deliveries. The immediate maternal mortality was 10 per cent.; seven of the twenty-five deaths were not, or were only questionably, due to eclampsia.

Remote. Post-toxæmic Hypertension The fall of pressure after delivery at one time gave rise to the comfortable belief that pre-eclamptic toxæmia was a completely reversible disease with no sequelæ, other than a slightly increased liability to a similar attack in a subsequent pregnancy. Harris (1924), however, examining patients one year after they had been discharged free of symptoms, found that of

7 who had had eclampsia, three had signs of "chronic nephritis", and of 55 who had had pre-eclampsia, 33 had signs of "renal involvement." In the same year, Kellogg (1924) drew attention to what he called recurrent toxæmia of pregnancy, "a great group of cases which, though showing no clinical manifestations of chronic nephritis when not pregnant according to the ordinary methods of clinical observation, nevertheless, in all or in the majority of pregnancies, showed kidney insufficiency or toxic manifestations." Gibberd (1929) found that after toxæmia, 10 per cent. developed "chronic nephritis," 40 per cent. recovered kidney function completely and 50 per cent. were well between pregnancies but developed proteinuria in subsequent pregnancies. However, the modern phase of our knowledge begins with Herrick and Tillman (1935) representing collaboration between a physician and obstetrician. They reported the results of a six-monthly examination by a physician of 594 women who had had toxæmia of pregnancy. They found that the death rate in these women was seven times the average death rate for women of childbearing age, and that 80 per cent. of the deaths were cardiovascular. They felt that there were two basic diseases, primary nephritis and primary hypertension on which toxæmia became superimposed. Of their patients, they found that 30 per cent. had a blood pressure of over 150 at the end of a year of follow-up, while after three years the proportion had risen to 80 per cent. Proteinuria was variable but present in 20 per cent. Oedema was rare. Eleven patients came to necropsy, the diagnosis being glomerulonephritis in four and primary cardiovascular disease with arteriosclerosis in seven. Reading through these cases and autopsy reports, four would seem to be cases of chronic pyelonephritis, three of chronic nephritis, two of malignant and two of benign essential hypertension.

... .. toxæmia of pregnancy. One hundred and forty-four of these were classified as pre-eclamptic toxæmia. 73 or 51 per cent. on follow-up examination had hypertension, i.e. a blood pressure over 130/70. Of those without hypertension 31 became pregnant again, and of these 20 developed recurrent toxæmia. The incidence of post-toxæmic hypertension was influenced by the height of the blood pressure during pregnancy, the duration of the toxæmia before delivery and the blood pressure on discharge, very slightly by age and parity. Forty-six patients had had eclampsia; hypertension subsequently occurred in 61 per cent., 65 per cent. died. If they used 140/90 and not 130/70 as the index of hypertension, 30.5 per cent. of the patients who had had eclampsia showed hypertension in the follow-up. They concluded that the younger the eclamptic patient, the less pregnancies she had had, the fewer the fits, the lower her blood

The infant mortality and stillbirth rate in 27,000 deliveries at the Bellevue Hospital, New York, are shown in Table 23.2. We may conclude from these figures that the earlier in pregnancy that toxæmia develops the less likelihood there is of a living child. Exacerbation of hypertension and in particular the development of eclampsia increase the rate of stillbirths.

MORBID ANATOMY OF PRE-ECLAMPTIC AND ECLAMPTIC TOXÆMIA

Sheehan (1950) has devoted especial attention to this subject and his account of the brain has already been quoted.

Kidneys. The most constant changes are in the kidneys. In early cases the glomeruli are enlarged and point into the necks of the tubules. Their endothelial cells are swollen, and lay down fine fibrils under the basement membrane or between the cells; these fibrils give the staining reaction for collagen. The first convoluted tubules show occasional hyaline droplets in their cytoplasm; the collecting tubules often show considerable cast obstruction sometimes of protein type, but sometimes of hæmoglobin derivatives. Cast obstruction probably occurs chiefly in those patients who have oliguria.

In eclampsia in multiparæ or elderly primiparæ, where the syndrome develops at six months, these changes are exaggerated. An occasional glomerular capillary loop enlarges until it comes into contact with the capsule. When this happens, the basement membrane and the endothelial fibrils in the loop swell up and become a coarse hyaline network with staining reactions different from those of the original structures. The epithelium of the loop and the capsule proliferates at the site of adhesion and there forms a small crescent. The afferent arteriole outside the glomerulus frequently has small localized swellings of its internal elastic lamina like small hyaline beads. The media of the arteriole is sometimes hyalinized.

In some patients showing the clinical manifestations of malignant hypertension, the kidneys show the changes of the malignant phase superimposed on those of the eclamptic lesions. There is fibrinoid necrosis of the arterioles associated with various degrees of glomerular infarction. There may be older hypertensive lesions.

Liver. The liver is the other organ most commonly affected. The characteristic feature is the presence of periportal hæmorrhagic lesions. The blood tends to push up the columns of liver cells, with necrosis of the cells at the lower end of these columns, where they are in contact with the blood. In other cases, the liver lesion is more diffuse. The plasma or blood bursts in the same way from the sinuses into the base of the liver column. The liver cells are pushed up and necrotic.

... so that

they form a thin band down the centre of the artificial blood channel. The diffuse lesion probably is characteristic of a severe eclampsia that is always fatal.

Hæmorrhages are found also in the lungs, under the endocardium of the heart, and in the suprarenals.

The Placenta. Normally, the placenta is an ageing organ as term approaches, and a variable amount of pathological change is found in many normal pregnancies.

Infarcts of the placenta seem to be commoner in toxæmia of pregnancy than in normal pregnancy. To quote Young (1914) "Meyer found them in 2 per cent. of 1,124 placentæ, Rossier in 17½ per cent. of 1,174, whilst Whitridge Williams found white infarcts, measuring 1 cm. or more in diameter, in 63 per cent. of 500 placentæ. Such figures, though exhibiting a wide margin of difference, leave no doubt regarding the relatively high frequency of the condition. On the other hand, there can be equally little doubt that these changes are associated in some special manner with the toxæmias, albuminuria and eclampsia. In Rossier's figures given above 54 of the women suffered from albuminuria, and, in these, infarcts were three times more common than where the urine was healthy. In Meyer's patients, where albumin and casts were present, infarcts were four times more frequent than where there was a normal urine. Fehling found them in 50 out of 91 albuminuric patients The infarcts, which are of greatest importance . . . are those of the recent or red variety."

These infarcts represent solid areas in the foetal portion of the decidua. The white infarcts are attributed to obliterative endarteritis which shuts off the foetal circulation to the affected area (Bartholomew and others, 1949). The red infarct is due to hæmorrhage and villous degeneration. Kellogg (1945) was the first to suggest that intimal thickening, closely resembling atheroma, affecting the maternal arteries, caused spontaneous rupture and extravasation of maternal blood.

Zeek and Assali (1950) found the most common obstructive vascular lesion in cases of placental infarction was acute atherosclerosis of decidual vessels, especially endometrial spiral arteries and endometrial venous lakes, found in 30 per cent. of the 70 cases with infarcts. This lesion was characterized by the deposition of large amounts of fatty material in the intima of decidual vessels, appearing first within large mononuclear foam cells similar to the lipophages described by Leary in cholesterol atheroma in rabbits. Later a fibrinoid necrosis and polymorphic type of inflammatory exudate are found. Atheroma of decidual vessels was present in 34, absent in 37 cases of toxæmia; present in three, absent in 140 cases without toxæmia; present in none, absent in 18 cases with hypertension but without toxæmia. They

consider that placental infarcts, which they found closely associated with toxæmia, are due to these obstructive lesions of maternal vessels.

There is fairly general agreement that infarcts of the kind described are commoner in "toxæmias," whether or not complicating pre-existing hypertension or renal disease, than in normal pregnancy. Nevertheless, it is generally agreed that sometimes these lesions are not found in toxæmia, and, that they are also found in normal pregnancy.

Tenney and Parker (1940) claim that the characteristic placental lesion in toxæmia is a syncytial degeneration of the terminal villi, which occurs in 10 to 50 per cent. of villi in normal pregnancy, in the majority of villi in toxæmia, and in all the villi in severe pre-eclampsia and eclampsia. This they found a much more accurate guide to the presence or absence of albuminuria than the prolan content of the placenta or urine.

THE CIRCULATION IN PRE-ECLAMPTIC TOXÆMIA AND NORMAL PREGNANCY

Cardiac Output. Using the older gas methods, the cardiac output was found to rise through pregnancy and to fall afterwards. Making repeated determinations in four trained patients, Burwell and others (1938) found, however, that the cardiac output fell to approach pre-pregnant levels during the last four weeks of pregnancy. Very much the same results were obtained by Hamilton (1949) determining cardiac output by the Fick principle and the use of the cardiac catheter. She found the cardiac output in resting basal non-pregnant woman was 4.5 litres a minute. Output began to rise about the tenth week of pregnancy, reached a maximum of 5.8 litres at twenty-six to twenty-nine weeks and then fell to average 4.6 litres at thirty-eight to forty weeks, thereafter remaining normal during the

hypertension. Palmer and Walker (1949) found no evidence of a terminal fall in cardiac output in normal pregnancy. Werkö (1950) and his colleagues find little difference in cardiac output in the later stages of pregnancy between normal

normals, normal 7.1, pre-eclampsia 7.3 and hypertension 7.4.

Blood Volume. The blood volume rises in pregnancy and this rise is associated with a fall of hæmatocrit; the blood volume in hypertension is essentially the same as in normal women, while that in

they form a thin band down the centre of the artificial blood channel. The diffuse lesion probably is characteristic of a severe eclampsia that is always fatal.

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Assali and others (1953) have measured the uterine blood flow by a modification of Kety's nitrous oxide method, catheterizing the uterine vein in normal pregnancy. During the last month of pregnancy the uterine blood flow averages 15 ml. per 100 gm. per minute and falls to 9 ml. within the first twenty-four hours after delivery.

Limbs. Burt (1950) has shown that the muscle blood flow, as estimated plethysmographically in the forearms, is slightly increased in pregnancy, and there is an even greater increase in women with pre-eclamptic toxæmia; these differences persist when the feet are immersed in hot water. The skin temperature of hands and feet also tends to be increased.

Comment. If we accept the view that the cardiac output is much the same in pre-eclamptic toxæmia as in normal pregnant women, then we must conclude that the raised arterial pressure is due to increased peripheral resistance. On the other hand Hamilton's results suggest that cardiac output may be a factor. . . . we may conclude provisionally that distributed; renal, hepatic and cerebral flow are little altered, muscle flow may be increased and uterine flow decreased. Clearly there is no evidence whatsoever for the idea that the anatomical changes in kidney and liver are due to ischæmia; nor is there evidence of cerebral ischæmia.

Blood Pressure Responses in Toxæmia

A great deal of work has been done to discover to what extent the blood pressure responses to various agents are altered in patients with pregnancy toxæmia. Unfortunately, there is some discrepancy amongst results obtained by different authors. Moreover, it is not easy to interpret the results. Thus Dieckmann and others (1938) found that of 90 "hyper-reactors" to the cold pressor test (see p 147), 31 per cent. developed toxæmia, while of those who gave a normal response, only 3 per cent. developed toxæmia.

... , while of those
... it was 14.1 mm. Most workers seem agreed, however, that patients with pre-eclamptic toxæmia show an unusually large rise of blood pressure to injection of post-pituitary hormone (Schockaert and Lambillon, 1937, Dieckmann and Michel, 1937, Browne, 1943). Two recent papers may be quoted from the very large number published. Werkö and Brody (1953a) obtained two-hourly readings of arterial pressure in 108 cases of toxæmia of pregnancy (arterial pressure over 160/100 on two ...).

eclampsia tends to be lower than normal (White, 1950). Similar results were described by Werkö (1950). That the hæmatocrit falls in pregnancy would lead us to suspect that blood viscosity would change in a similar direction, and such seems to be the case (Kellar, 1950a).

Liver Blood Flow. Using the bromsulphalein method, Munnell and Taylor (1947) found that the hepatic blood flow was much the same in pregnant and non-pregnant women. In a small series of patients with essential hypertension, chronic nephritis and toxæmia of pregnancy, the liver blood flow was normal or slightly raised.

Brain. Using Kety's nitrous oxide method, McCall (1949, 1953) has shown that the cerebral blood flow remains essentially within normal limits in pregnancy, and in those pregnant women who have hypertension or pre-eclampsia.

Kidney. The renal circulation has been investigated, using the well-known clearance methods of Smith and his colleagues for glomerular filtration rate and effective renal blood flow. There is in general a fair agreement between the findings of different workers. Corcoran and Page (1941) found a reduced inulin clearance (C_{IN}) and a normal diodone clearance (C_D), the former increasing, the latter falling, after delivery. They attributed this to thickening of the glomerular basement membrane. In essential hypertension and pregnancy, they observed the usual increase of filtration fraction. Wellen, Welsh and Taylor (1942) found a normal C_{IN} which rose after delivery and a normal C_D which was unaltered by delivery. Bucht and Werkö (1953) found that in 28 cases of hypertensive toxæmia the inulin clearance was less than in normal pregnancy at the same stage, and that it rapidly increased after delivery. The PAH clearance was also reduced, and rose more slowly after parturition and in some cases did not rise at all. Although Bucht and Werkö conclude that the decreased glomerular filtration rate is not of organic origin, it would seem exactly what would be expected from the increased thickness of tissue that lies between the glomerular capillary lumen and the capsular space, and this explanation may be accepted.

Uterus. Browne and Veall (1953) have made estimates of the rate of removal of Na^{24} injected into the maternal blood pool of the placenta, from which they suggest that in women with hypertension the placental blood flow may be reduced. However, the observations are not easy, and the results are to be accepted with caution. Thus, of 274 cases in which the placenta was located on the anterior abdominal wall, curves for the rate of disappearance of Na^{24} were obtained only in 25; of these 10 were rejected for technical reasons, leaving eight subjects with normal pressure in whom the half-period for the removal of radioactivity was twenty-one seconds and seven subjects with raised pressures in whom the corresponding half-period was sixty-five seconds.

It has long been believed, and is generally accepted, that the following factors predispose to pre-eclampsia (see for example, Page, 1953).

- (1) A first pregnancy.
- (2) Body build : short and fat.
- (3) Multiple pregnancy : triplets more than twins.
- (4) Hydramnios.
- (5) Essential hypertension.
- (6) Chronic nephritis.
- (7) Diabetes.
- (8) Severe anemia.
- (9) Beri-beri.
- (10) Hydatidiform mole (after the fourth month).

Taken as a whole, these factors suggest that the occurrence of toxæmia of pregnancy is dependent upon two factors, the sensitivity of the vascular system, and the conditions in the uterus. So far as the latter is concerned, the very frequent occurrence of toxæmia in that curious condition hydatidiform mole, in which there is no foetus, again suggests the placenta as the locus of the primary disturbance.

A similar conclusion is reached from a consideration of the circulation of the child. Browne and Dodds (1936) measured the blood pressure of the infants two to 18 days old of six normal and three toxæmic women. The average systolic pressure of the normal infants was 73 mm Hg, of the infants of toxæmic women 75 mm. Hg, though the mothers all had pressures above 200 mm. Hg. Woodbury, Robinow and Hamilton's (1938) figures for the infants of twenty-four normal and eight toxæmic women were $80 \cdot 1/40 \cdot 3$ and $90 \cdot 5/49 \cdot 9$. Dexter and Weiss's (1941) systolic figures obtained immediately after delivery for infants of mothers with normal and raised pressures were $70 \pm 10 \cdot 5$ mm and $78 \pm 12 \cdot 3$ mm. respectively. Thus it would seem difficult to attribute the

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to substances which fail to pass the maternal-foetal barrier, and are, therefore, of large molecular size. However, such a suggestion must be advanced with caution, because many of these observations on the child have not been made immediately after birth and the child may

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placental infarcts are common in toxæmia. These may be part of the

¹ Moreover the reader will note that although none of these differences are significant, the higher pressures are in each case found in the infants of mothers with hypertension.

found that the variability was less in patients with pregnancy toxæmia than in patients with essential hypertension having eyeground changes of similar extent, and considered this indicated a different mechanism. On the other hand, the pregnant women were younger than the patients with essential hypertension and their blood pressures were on the whole lower; moreover, toxæmia represents a recent, essential hypertension \blacksquare chronic, hypertension.

The same authors (1953b) found that sodium amytal, sodium nitrite and dehydroergocornine caused small falls of blood pressure to levels comparable to the lowest found spontaneously. Tetra-ethyl-ammonium salts and veratrine gave larger and approximately equal responses; these responses were augmented when sodium excretion was increased, and the body weight reduced.

These responses are so complex that, even if we knew the separate behaviour of cardiac output and peripheral resistance to each drug, it would be far from easy to decide what they meant.

ÆTIOLOGY OF PRE-ECLAMPTIC TOXÆMIA

The vast literature on the ætiology of toxæmia cannot be reviewed here. The reader is referred to Dexter and Weiss (1941), Browne (1944), Kellar (1950b) and Page (1953).

Attempts have been made to explain the whole symptom-complex by a single disturbance, such as vascular spasm or sodium retention. The former finds no support from actual measurements of blood flow; nor does it account for proteinuria¹ or œdema. As for the latter, it occurs in hypoproteinuric œdema and cirrhosis without hypertension. It would seem better to recognize that the ætiological factors are likely to evoke a fairly definite type of somatic response without arriving at premature conclusions as to the precise channel through which that response is effected. So far, the facts to be accounted for are as follows. The syndrome consists of three essential manifestations, hypertension, proteinuria and œdema. The anatomical lesions in kidney and liver cannot be ascribed to the hypertension or to an underlying vascular spasm. The œdema is an exaggeration of a process that is found in more than half of pregnant women. Finally, the whole disturbance tends to disappear with parturition, an event that may be attributed most probably to discharge of the placenta.

¹ catheter at minute intervals. proteinuria is old. The only who immersed the hands of urine was collected from a I no increased excretion of mules: of these only two had rises of blood twenty-three had an increase of proteinuria: 16/16 mm. Hg. Unfortunately, no ages are

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Taken as a whole, these factors suggest that the occurrence of toxæmia of pregnancy is dependent upon two factors, the sensitivity of the vascular system, and the conditions in the uterus. So far as the latter is concerned, the very frequent occurrence of toxæmia in that curious condition hydatidiform mole, in which there is no foetus, again suggests the placenta as the locus of the primary disturbance.

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primary disturbance in toxæmia As we have seen, placental infarcts are common in toxæmia. These may be part of the

* Moreover the reader will note that although none of these differences are significant, the higher pressures are in each case found in the infants of mothers with hypertension.

more general vascular disturbance seen in kidney and liver, or they may be the result of a primary placental disturbance. A prevalent conception put forward by Young (1914) is that interference of blood supply to the decidua and placenta leads to the liberation of some toxic substance. However, extracts of placentæ obtained from women with toxæmia have not yielded pressor responses (Dexter and Weiss, 1941).

The hypothesis that, in some way, a reduction in the blood supply to the gravid uterus is the essential cause of toxæmia of pregnancy has long been popular and has been particularly espoused by Beker (1948), Page (1953) and by Van Bouwdijk Bastiaanse. Ogden, Hildebrand and Page (1940) and Van Bouwdijk Bastiaanse and Mastboom (1950) have both shown in acute experiments that constricting the arteries to the pregnant uterus causes a rise of systemic arterial pressure, whereas constricting the aorta distal to the renal arteries in normal dogs does not. These observations should be repeated as chronic experiments. It will soon become apparent whether the rates of blood flow through the uterus in general, and the placenta in particular, in women with and without toxæmia are compatible with this hypothesis.

It is known that the placenta participates in the manufacture of hormones and that the normal conduct of pregnancy is intimately dependent on a rather complex change in the amounts of these substances secreted from pituitary, ovaries, placenta and adrenals into the blood. There is a prevalent idea, to which I subscribe, that the most probable cause of toxæmia is a change in the pattern of these hormones. However, methods of identification and assay are still in an early stage and no final conclusion can yet be reached.

Posterior-pituitary Substance. This was an early favourite since it produced a rise of arterial pressure and retention of water in the experimental animal. The experiments of Anselmino, Hoffmann and Kennedy (1932), in which they claimed to have demonstrated posterior pituitary substance in ultrafiltrates of plasma, were not confirmed by many workers reviewed by Browne (1944). In man, the antidiuretic effects are so much more striking than the pressor effects that pitressin does not seem a very likely effective agent. However, the careful experiments of Ham and Landis (1942) showed that the placenta of patients with toxæmia of pregnancy contains an anti-diuretic substance that is not found, at any rate with the same frequency, in normal placentæ. This antidiuretic substance is also present in the urine in greater amounts in women with toxæmia than in those without; and the amount lessens after parturition. The properties of this substance differ from those of posterior pituitary hormone in certain respects; thus it does not dialyse, behaves as a larger molecule in the ultra-centrifuge, and does not increase chloride excretion in the urine. On general principles, it would seem probable that the œdema of pre-

eclamptic toxæmia is due to the presence in the body of an antidiuretic substance, whose amount abruptly lessens with discharge of the placenta.

Adrenaline and Noradrenaline produce effects quite unlike the changes in specific hypertensive disease of pregnancy. Bucht and Werkö (1953) found the urinary excretion increased in one and normal in one case.

Renin and Hypertensin. Dexter and Haynes (1944) found an excess of renin in the blood in three out of eight women with toxæmia of pregnancy. As we have noted, all these observations need repeating with better methods.

Chorionic Gonadotrophin Smith and Smith (1948) reported an abnormally high level of chorionic gonadotrophin in the urine of women suffering from pre-eclampsia, and their work has been repeated with varying results. Loraine (1949b, 1950) gives the following figures. During normal pregnancy, the chorionic gonadotrophin rises to a peak before the 100th day; afterwards, the urinary excretion is less than 10,000 i.u. per day. In some cases of pre-eclampsia the excretion may rise to 18,000 or 20,000 i.u. per day. The serum level also rises (Loraine and Matthew, 1950). However, there is no correlation between the severity of pre-eclampsia and the gonadotrophin level. Moreover, a high gonadotrophin level is usual in diabetic pregnancies, and there is no relationship between that level and obstetric complications such as pre-eclamptic toxæmia (Loraine, 1949a).

Œstrogens The error in the estimation of these substances is still very large, but it appears that the Œstrogen content of blood, placenta and urine in toxæmia is low. For example, Watts and Adair (1943) found the excretion of total Œstrogen in later pregnancy was 30,200 i.u. in normal women and 17,820 i.u. in toxæmia.

Progesterone is excreted in the urine largely as pregnanediol whose excretion rate appears to be less in women who have toxæmia than those who do not. De Watterville (1931) has found that the values in those women who were delivered of a normal and well-developed infant, were higher than in women whose child was underdeveloped or stillborn. It seems, therefore, that the excretion rate of this substance is chiefly dependent on the state of the placenta.

Smith and Smith (1948) have produced a long series of papers which have led them to the view that pre-eclampsia is caused by a tissue poison liberated by a failure in maintenance of the placenta and decidua, the placental degeneration leading to certain abnormalities of steroid and gonadotrophin excretion. They have obtained from menstruating endometrium an atypical euglobulin which is fatal in small doses. They believe

A. uterus

when hormonal support is withdrawn, and that release of this toxin may prove to be the final cause of toxæmia of pregnancy.

Adrenal Corticosteroids. Since DCA in large doses is known to produce œdema and hypertension in man, a derangement in cortical steroids has been a favourite hypothesis to explain the phenomena of pre-eclamptic toxæmia. The estimation of these substances has, however, been troublesome, and it is only recently that their excretion in toxæmia has been measured. Devis and Devis van den Eeckhoudt (1949), Parviainen and others (1950) and Chart and others (1951) agree that the excretion of some of these substances is raised in toxæmia of pregnancy. These substances can now be estimated fairly accurately in both blood and urine by chromatography and new information should soon be to hand.

Comment. It would seem clear that there is a complex disturbance in the hormonal content of blood, and in the urinary excretion of hormones, in toxæmia of pregnancy. What is not yet clear is how far these changes are causally related to the phenomena in the mother and the effects on the fœtus. However, quantitative endocrinology is in its infancy, and it would seem to the writer that the next few years may revolutionize our ideas on this subject.

THE TREATMENT OF PRE-ECLAMPTIC AND ECLAMPTIC TOXÆMIA OF PREGNANCY

Antenatal clinics are designed so that pre-eclamptic toxæmia, amongst other hazards of pregnancy, can be recognized and dealt with early. The earliest signs may be an increase in œdema beyond that accepted as physiological, i.e. a weight gain of over 2 lb. a week (Page, 1953), a rising arterial pressure, or the appearance of proteinuria. A pathological weight gain by itself is generally treated by a restriction of salt intake to less than 3 grammes per day, and is, by this simple measure, usually controlled. In more resistant cases, ammonium chloride 6 to 12 grammes (in gelatin capsules) each day for three days may provoke a satisfactory diuresis. A rising arterial pressure may be satisfactorily controlled by phenobarbitone or other sedative together with a rest period every afternoon. Proteinuria, appearing in conjunction with the other disturbances, requires a more watchful attitude. In mild cases the measures prescribed result in an amelioration of symptoms. In severe cases, the condition progresses, and it is essential now to put the patient to bed, preferably in hospital, while continuing the same general measures. If the patient is near term, labour is now induced by rupture of the membranes. But if the patient is some distance from term, the decision as to whether or not to terminate pregnancy will be taken after considering the following points:

- (1) The behaviour of the patient's cardiovascular system. If the

arterial pressure does not rise above, say, 150 systolic, there is a case for allowing pregnancy to continue. The following are ominous signs which suggest that pregnancy should be terminated: (a) an abrupt rise of 40 mm. Hg systolic or 20 mm. Hg diastolic, (b) the sudden appearance of massive proteinuria; (c) the appearance of papilloedema or exudates in the fundus oculi; (d) severe continuous headache, drowsiness or irritability indicating the possible supervention of eclampsia; (e) oliguria with rising blood urea; (f) left ventricular failure.

(2) The nearness to term. As we have seen, the duration of toxæmia may determine whether or not the patient has a post-toxæmic hypertension. If the toxæmia begins so early that the mother's future may be jeopardized if pregnancy is allowed to continue till the child will be viable, then pregnancy should be terminated at once. On the other hand, if the child is viable and the toxæmia under control, it may be decided that the risk to the mother is worth the possibility of obtaining a more mature infant.

Cosgrove and Chesley (1948) summarize the management of pre-eclampsia as follows: "Progressively severe 'true' pregnancy toxemias whether engrafted on pre-existing hypertension or not, must not be temporized with. Ruthlessly radical termination of pregnancy serves alike the interest of mother and fetus. The convulsive toxemias should be treated wholly along conservative medical lines without artificial interference with the pregnancy. Recovered convulsive toxemias should have the pregnancy terminated exactly as in the severe progressive non-convulsive types."

The supervention of eclampsia alters the picture, as the chances of a living child diminish. The mother is nursed in a quiet dimmed room and treated with sedatives such as morphine and barbiturates. No attempt should be made, in any way, to interfere with pregnancy. When the convulsions have been controlled for at least twenty-four hours then pregnancy should be terminated.

That the patient can be brought out of an eclamptic fit with extracts of *veratrum viride* has long been known. It is now apparent that the *veratrum* alkaloids, hexamethonium and pentapyrrolidinium, given in doses to produce falls of arterial pressure, can control the convulsions of eclampsia. The author prefers methonium prep. in all cases of eclampsia.

It was hoped that control of arterial pressure by the new drugs described in Chapter 15 would vastly improve the outlook for both mother and child in toxæmia of pregnancy. Such, unfortunately, seems not to be the case. Stern and Burnett (1954), reviewing the effects of different forms of treatment, found that maternal and foetal

mortality were respectively as follows : with sedation 7.56 and 29.17 per cent. ; with sedation and hypotensive treatment (bromethol) 4.03 and 32.58 per cent. ; with hypotensive treatment (veratrone) 1.81 and 28.46 per cent. Clearly, veratrone seems greatly to have improved the outlook for mother, but not that for child. Morris (1953) treated 32 pregnant women with hypertension of different kinds by hexamethonium. Control was more effective by injection than by mouth. Seven infants were stillborn, twelve born alive, but of these no less than seven died within eight days ; two of them had gross, intestinal dilatation. Hexamethonium passes freely into the amniotic fluid, and some of the ill-effects on the child may be due to swallowing of the fluid.

III. PREGNANCY IN THE WOMAN WITH HIGH BLOOD PRESSURE

In this section we are concerned with the effects of pregnancy in a woman who has an elevated blood pressure, or who, during pregnancy, develops a disease (unconnected with pregnancy) which causes high blood pressure. The second of these alternatives is rather uncommon, and is chiefly troublesome because it may be confused with specific hypertensive disease of pregnancy.

Arguing from first principles one would expect that the frequency of different types of hypertensive disease complicated by pregnancy would be approximately the same as their frequency in women of the same age in the general population. This is probably approximately true. The order given in Table 23.1 is probably not far from being true to-day, but neither author included chronic pyelonephritis which, I suspect, is a little commoner nowadays than chronic nephritis ; for which, as we have seen, it may be mistaken. Little need be said of the effect of pregnancy on the less common forms of hypertension, except those due to disease of the suprarenal gland, which have been reviewed by Hunt and McConahey (1953). They point out that pregnancy is very rare in Cushing's syndrome, and that in this condition abortion is common. They report five pregnancies in three patients with adrenal hyperplasia, and one pregnancy in one case with a cortical tumour. These resulted in one abortion, one foetal death and four living children. In pheochromocytoma, pregnancy seems to be very dangerous to both mother and child. There are now seven recorded cases with nine pregnancies. Two mothers died post-partum of shock. Five of the nine foetuses died.

ESSENTIAL HYPERTENSION

The effect of pregnancy on patients with essential hypertension has been especially studied by Browne (1947) and Chesley and Annitto (1947). The former accepts 120/80 as the dividing line, the latter

140/90 These workers on each side of the Atlantic broadly agree ; since, however, Chesley and Annitto give detailed figures, their account will be followed. Table 23.3 shows the relationship of the first recorded pressure to the subsequent events. As Reid and Teel (1939) first pointed out, a fall of pressure is usual in the second three months of pregnancy. In Chesley and Annitto's cases, a fall of 20 mm. Hg occurred in 39.6 per cent, of 40 mm. or more in 11.6 per cent., and in 50 per cent. there was no change. As Table 23.3 shows the fall was

TABLE 23.3. *Summary of Pregnancy and Follow-up Findings in 218 Hypertensive Women having 301 Pregnancies at the Margaret Hague Maternity Hospital (Chesley and Annitto, 1947).*

Initial Systolic Blood Pressure mm. Hg	140 to 159	160 to 179	180 to 199	200 or more	Totals
Based upon Pregnancies					
Total pregnancies	123	92	43	43	301
First recorded blood pressure :					
Pre pregnant, cases	28	32	16	15	91
First trimester, cases	24	22	7	6	59
Second trimester, cases	65	25	13	16	119
Third trimester, cases	6	12	7	7	32
Proportion with midpregnancy drop in blood pressure (106 cases), per cent.	28.9	48.4	56.3	42.9	39.6
Blood pressure near delivery, compared with initial recording :					
Lower, per cent	1.8	31.5	36.8	40.5	20.8
Same (\pm 20 mm. Hg) per cent.	55.8	43.8	39.5	43.7	40.1
Higher, per cent	42.4	24.7	23.7	10.8	30.1
Incidence of superimposed toxæmia in 149 cases with pre-pregnant or first trimester blood pressure recordings, per cent.	28.9	27.8	30.4	30.0	28.8
Fetal mortality, per cent.	31.7	32.6	39.5	67.4	38.2

least common in
 In the last three Hg.
 first recorded pre the
 same in 49 per cent. of cases. The final pressure tended to be higher
 than the initial, especially when the initial pressure was low, and tended
 to be lower than the initial, especially when the initial was high ; in
 the intermediate zone, the initial pressure

Annitto's (1947) experience was less uniform. As Table 23.3 shows, the incidence of "toxæmia" in the whole series (28.8 per cent.) was much higher than in the population at large, but was not, apparently, much affected by the initial level of arterial pressure. Table 23.4 shows the relationship between the systolic arterial pressure near delivery and proteinuria in Chesley and Annitto's series. The relationship is very striking, the probability of proteinuria increasing with the pressure until, above 220 mm. Hg systolic, proteinuria is invariable.

As regards foetal mortality Browne states: "In my last series of 194 cases between 1942 and 1946 . . . there were 48 multiparæ, who

TABLE 23.4. *Proteinuria in Relation to Degree of Hypertension (near delivery) in 300 Hypertensive Pregnancies (Chesley and Annitto, 1947).*

Systolic Blood Pressure mm. Hg	140 to 179	180 to 199	200 to 219	220 or more	Totals
Total cases	187	64	33	16	300
Urine normal, per cent.	66.8	36.0	12.1	0	50.7
Possibly significant proteinuria ("trace"), per cent.	11.8	10.9	18.2	6.3	12.0
Significant proteinuria, per cent.	21.4	53.1	69.7	93.7	37.3

between them had 78 pregnancies but only 27 live infants—a foetal loss of 65.3%. . . . These same 48 women in their present pregnancy—that is, the one under observation and supervision—produced 45 live and surviving infants—93.7%, a foetal wastage of only 6.3%. This may be a tribute to the value of antenatal care in these cases."

The relationship between the mother's blood pressure at the beginning of pregnancy, and foetal mortality is shown in Table 23.3. Foetal mortality rose from 32 per cent. with initial pressure 140 to 159 to 67 per cent. when the initial pressure was 200 or more. Table 23.5 shows the relationship between blood pressure near delivery to the fate of the foetus; here the relationship to blood pressure level is even closer. Wellen's figures for foetal mortality are given in Table 23.2. The very high rate of foetal death is one of the cogent reasons for not proceeding with pregnancy in women with hypertension, particularly in those with high initial pressures and, more especially, in those whose pressures rise to high levels late in pregnancy.

In Chesley and Annitto's (1947) series there were six immediate maternal deaths, a rate of 2 per cent. Two of those, due to eclampsia and cerebral hæmorrhage, may be attributed to the hypertension. There were also seven late puerperal deaths, six weeks to four months post-partum. Four died of malignant hypertension, one of acute endocarditis, one of acute heart failure and one sudden death.

The remote prognosis to the mother was studied by Chesley, Annitto and Jarvis (1947) who followed up the 301 cases alluded to in tables 23.3 and 23.5. 17.9 per cent. of the patients had died in one to fourteen years, average seven years, the average age at death being 54 years. Their most important finding was that in those who had superimposed toxæmia, the death rate was 31.7 per cent.; in those who had not, the death rate was 9.6 per cent. As might have been expected the annual death rate was more than twice as high in those

TABLE 23.5. *Relationship of Blood Pressure near Delivery to Fatal Outcome in 301 Pregnancies in Women with Essential Hypertension. (After Chesley and Annitto, 1947.)*

Average Systolic Blood Pressure mm. Hg	Cases No.	Child discharged from hospital living, per cent.
140 to 159	109	81.5
160 to 179	75	64
180 to 199	61	43.9
200 to 219	33	45.5
Over 220	24	29.2

whose initial pressure exceeded 200 mm. Hg than in those with lower pressures.

Comment. It is not at all clear why the arterial pressure should rise in the late stages of pregnancy in some women with hypertension and not in others. Clearly it is more likely to rise in women with hypertension than in women with lower pressures. The absence of any relationship between the incidence of a late rise and initial pressure, once the hypertensive level has been passed, might be used, though so far as I know it never has been, as an argument for essential hypertension being a clinical entity. However that may be, this rise has two important consequences for the mother, (a) that she may develop proteinuria, after which, in common with women with initially lower pressures, her remote prognosis is worsened. It is not known whether this is a consequence of a late post-toxæmic exacerbation of hypertension, though my own unanalysed casual experience would lead me to suppose that this is so.

(b) That she may go into the malignant phase or develop one of the other complications of severe hypertension. It is also accompanied by a very high fetal mortality, most of this being due to placental infarction.

Management. In the past, when treatment for hypertension was ineffective, management was largely directed to ensuring that those

with the higher levels of pressure did not become pregnant, or if they did, or decided to take a chance because of an overwhelming desire for a child of their own,¹ to pilot them until a decision was reached to terminate pregnancy. The chief therapeutic measure was rest, an afternoon sleep in early and mild cases, complete bed rest in the severe, using barbiturates and common-sense psychotherapy as required. In this way, many a woman could be got to a stage when the foetus was viable. Delivery well before term and preferably from the thirty-sixth to the thirty-eighth week was desirable in the more severe cases, in order to obtain a living child, and thus before extensive placental infarction had occurred.

Newell and Smithwick (1947) reported a series of 28 women who had thirty-four pregnancies after splanchnicectomy. Only the 18 who began pregnancy with normal pressures did well. Of 10, whose arterial pressure exceeded 150 systolic and 90 diastolic, only two delivered living infants. Splanchnicectomy did not prevent the development of proteinuria.

It is still hoped that the new hypotensive drugs, particularly the methonium salts, will enable many more women with elevated arterial pressures to go through pregnancy satisfactorily. So far they have not increased the prospect of getting a viable child.

CHRONIC NEPHRITIS

To give an exact account of the influence of pregnancy on chronic nephritis is made difficult for three reasons: (a) that it is now an uncommon disease; (b) that the older accounts fail to distinguish this from other forms of hypertension in pregnancy; (c) the variable natural history of the disease. Of these causes, the last is by far the most serious and accounts for the extreme divergence of views of experienced obstetricians who hold, on the one hand, that pregnancy has a disastrous effect on chronic nephritis, and, on the other, that it has none.

Nephritis is diagnosed on the past history, on the discovery of protein in the urine early in pregnancy, on the gross excess of red cells, white cells and casts in the urine, and the other features detailed in Chapter 16. When the patient is seen late in pregnancy, the diagnosis may be difficult, and may not become clear till after parturition, when the persistent proteinuria and hæmaturia and, as a rule, defective renal function and the absence of the bacteriological and urographic signs of pyelonephritis and polycystic kidney make the diagnosis clear.

Many text-books teach that pregnancy should at once be terminated in chronic nephritis because of the deleterious effect upon the mother,

¹ In the past I am convinced that many doctors have failed to realize how important a child is to a woman. I have always taken the view that it is right to explain the risks and let her decide, explaining, of course, that it may all be of no avail because of the high foetal mortality.

and the slight chance of a living child. Addis (1948), however, stated: "As far as we can see, it (pregnancy) produces no qualitative change in the characteristic features of such diseases as glomerular nephritis, chronic pyelonephritis, or polycystic kidneys. . . . There is no instance in which we can be sure that the renal lesion interfered with pregnancy. There is no evidence that any of them have been harmed by pregnancy. . . . We mention this experience only because it supports the general evidence that pregnancy need impose no additional burden of work on the kidneys, and we are not saying that in other not yet comprehended ways pregnancy may not sometimes lead to renal catastrophe in patients with pre-existing renal lesions."

Apart from the ordinary hazards of nephritis, the chief additional risk is that of "toxæmia," which may here mean the supervention of the malignant phase—when pregnancy should be terminated at once.

Tilman (1951) followed 40 cases of glomerulonephritis. Of 10 cases of healed acute nephritis, one developed toxæmia and lost her baby, the remaining nine had normal pregnancies. Fourteen women with type 2 nephritis without hypertension went to term without complications. Of 16 women with chronic nephritis and hypertension, 11 developed acute pre-eclampsia and one eclampsia, one third of the babies were lost. It would seem that in the stage of chronic nephritis with hypertension the risk to the mother and the small chance of a living child alike indicate a therapeutic abortion.

PYELONEPHRITIS

Acute pyelonephritis usually due to *E. coli*, is a very common complication of pregnancy and is commonly ascribed to the ureteric obstruction produced by the pregnant uterus. It responds to the usual antibiotics.

Chronic pyelonephritis is probably a rather more common cause of hypertension and proteinuria of early pregnancy than is at present recognized. In some cases, it may prove impossible to sterilize the urine with antibiotics, and renal function may show a progressive decline. It is quite possible that here, too, the ureteric obstruction may interfere with antibiotic therapy and there is at least a case for terminating the pregnancy in the interests of the mother. In addition the patient with chronic pyelonephritis is subjected to the same hazards of superadded toxæmia and the development of the malignant phase.

SUMMARY

In most women with blood pressures in the lower range . . .

disease of pregnancy, or pre-eclamptic toxæmia of pregnancy ; when the hypertension is severe, hypertensive fits may occur and the condition is known as eclampsia. Specific hypertensive disease of pregnancy carries an immediate risk to the mother and to the child, the risk depending on the duration and severity of the hypertension and on the complications. Parturition is usually followed by a quick return of the arterial pressure to normal, and by diuresis and disappearance of œdema. In a considerable proportion of women the arterial pressure rises subsequently ; the incidence of this post-toxæmic hypertension seems to depend on the duration of the preceding "toxæmia." No definite conclusions have yet been reached concerning the mechanism either of specific hypertensive disease of pregnancy or of post-toxæmic hypertension.

In women who already have raised arterial pressures, pregnancy may be without effect on the intensity of hypertension, but is prone to produce a rise of arterial pressure in the last three months. When this rise of pressure is associated with the appearance of protein in the urine or an increase of proteinuria, it is usual to say that the hypertension is complicated by "toxæmia." In essential hypertension foetal mortality rises with increasing level of arterial pressure and with the incidence of toxæmia ; the remote prognosis to the mother is worsened by the occurrence of "toxæmia."

Because of the influence of the height of the arterial pressure and proteinuria on maternal and foetal mortality, and on the incidence of post-toxæmic hypertension in the mother, careful antenatal supervision is essential ; and if the arterial pressure cannot be controlled, termination of pregnancy may be indicated. The newer hypotensive drugs probably improve prognosis for the mother but not for the child.

The syndrome of the malignant phase of hypertension occurs in specific hypertensive disease of pregnancy at a lower level of arterial pressure than in patients with prolonged hypertension. The reasons for this are discussed.

CHAPTER 24

PRACTICAL POINTS IN THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH HIGH BLOOD PRESSURE

THE object of the physician in investigating disease is to obtain data concerning his patient's illness, that may be related to his own and other's experience of the probable outcome of the disease, and the extent to which that outcome is likely to be affected by treatment. The previous chapters of this book have attempted to set out established knowledge concerning the natural history of those diseases associated with high blood pressure, and their response to treatment. It may be helpful to some, particularly those with little practical experience, if we consider now the investigation of an individual patient with high blood pressure to see what can be done to help him.

In investigating a patient with high blood pressure, the doctor is particularly interested in the following questions :

- (1) Is the high blood pressure secondary to some recognisable lesion, and if so what is the nature of that lesion ? If no such lesion can be demonstrated, then the diagnosis of primary or essential hypertension is made by exclusion.
- (2) Is the high blood pressure in the benign or malignant phase ?
- (3) Are any of the known complications of high blood pressure present, particularly those relating to eye, brain, heart and kidneys ?
- (4) Is there evidence of associated vascular disease ?
- (5) Is any other disease not related to high blood pressure present ?

It is always possible to answer with some degree of precision at least

in part it is answered by other means of investigation, and in part it remains unanswerable by our present methods. The answer to the fifth question may be of as great, or greater, importance than the others, but for obvious reasons cannot be discussed here. It is mentioned merely to preserve that sense of proportion which is essential to sound practice.

DIAGNOSIS

Clinical Examination

In describing the investigation of a patient with high blood pressure, my chief object has been to be brief, since previous chapters have dealt with the relevant problems in some detail. Practical medicine is in part a matter of following clues, and it has therefore seemed convenient to give a brief outline, as it were a thumb-nail sketch, of the chief features of a disease at that point in the history or examination when the first or most important clue is obtained. Such a procedure is necessarily arbitrary, and to prevent misunderstanding it should be remembered that there is much variety in the way in which patients with a particular disease present themselves. Since this account is designedly brief, it is also incomplete, and is to be regarded merely as a guide which may be helpful in most, but not all, cases.

The general appearance of the patient, as the doctor first sees him or her, is of considerable importance, in *phaeochromocytoma* if the patient is seen in an attack and especially in *Cushing's syndrome*. In *Cushing's syndrome*, the face becomes red and rounded, the cheeks and lower jaw being filled out, and hair tends to grow freely on the beard area and on the body generally and to fall out on the scalp. Other findings are obesity, which tends to involve trunk more than limbs, purple striae, bruises, amenorrhœa, loss of libido, diabetes and osteoporosis, frequently leading to pathological fracture.

The sex of the patient is important in diagnosis only so far as hypertension is related to pregnancy (Chapter 23). Women withstand a given degree of hypertension better than men.

The age of the patient is very important. Severe hypertension in young subjects is nearly always secondary. The youngest age at which I have personally encountered malignant hypertension is eight years, in a girl with a congenital renal abnormality and bilateral pyelonephritis.

The occupation of the patient is not of much importance in diagnosis, but may be in management. Lead poisoning is now uncommon and its association with high blood pressure not established.

The present history is of great importance in indicating the cerebral, cardiac, ocular and renal complications of hypertension. Headache,

than without hypertension, but I think this is a "clinical impression. Transient and persistent losses of cerebral function suggest cerebral vascular disease, so does impairment of memory and deterioration of personality. Breathlessness on exertion suggests cardiac insufficiency and severe breathlessness at night cardiac asthma. Sternal pain may be diagnostic of angina pectoris or suggestive of myocardial infarction. Impairment of vision may be retinal or cerebral, as examination will

disclose Renal impairment is suggested by nocturnal polyuria, and in its later stages by nausea and vomiting and the other manifestations of uræmia.

As regards the basic lesion, the present history sometimes provides the most suggestive evidence of two diseases, *phæochromocytoma* and *polyarteritis nodosa*. In *phæochromocytoma*, the distinctive attacks comprise palpitations, cold blanched skin, headache, sweating, goose-skin, thoracic and abdominal pain, breathlessness and severe apprehension or fear; during the attack the arterial pressure is greatly raised, the skin blanched and cold and there may be a thyroid swelling; after the attack the patient is exhausted and the blood pressure may be very low; other findings are the extremely variable blood pressure and evidence, clinical or radiological, of an abdominal tumour; the diagnosis is clinched by the abnormal excretion of catechol amines in the urine. In *polyarteritis nodosa* the history of fever, loss of weight and strength, muscle pains and symptoms suggesting involvement of many systems is strongly suggestive; fever, leucocytosis, a high erythrocyte sedimentation rate and focal lesions of more than one system, support the diagnosis which is proved by biopsy.

The family history may be suggestive of polycystic kidneys in that siblings, a parent, and that parent's brothers and sisters, may have had kidney trouble or abdominal tumours. A history of high blood pressure, or of death from stroke or cardiac asthma in parents or siblings is suggestive that inheritance contributes to the hypertension. Cardiac failure, or angina pectoris, in parents and siblings suggests that the family may be disposed to atheroma. Too much importance should not be paid to such considerations because of the likelihood of fortuitous associations in conditions so common as high blood pressure and heart failure.

The past history is particularly important in suggesting the presence of a renal lesion. A history of hæmaturia and oedema suggests acute (Type 1) nephritis. A history of prolonged oedema suggests Type 2 nephritis. Frequency, urgency, smarting on urination, renal pain and fever suggest pyelonephritis. Hæmaturia or renal pain suggest a lesion in the urinary tract, such as growth, polycystic kidneys, *polyarteritis nodosa*, stone, intermittent hydronephrosis (hæmaturia rare) or other renal abnormality. A history of polyuria suggests renal impairment and may give a fair indication of its duration.

Physical Examination

The general appearance has already been noted.

In the cardiovascular system the presence of distended pulsating neck veins, breathlessness and

failure. In patients who have breathless attacks at night, gallop rhythm and pulsus alternans should be sought with especial care, in view of their indicating left ventricular failure. The size of the heart, assessed clinically and especially radiologically, is an important guide to prognosis. Auscultation may reveal, apart from gallop rhythm, the diastolic murmur of aortic regurgitation which in itself causes elevation of systolic but not diastolic pressure. Aortic regurgitation may be due to rheumatism or syphilis; or it may rarely be a complication of the hypertension due to simple dilatation of the aorta or to dissecting aneurysm. The height of the blood pressure is important for prognosis, and for diagnosis to the extent that severe hypertension in young subjects is nearly always secondary, and that severe hypertension suggests the supervention, present or future, of the malignant phase. Variability of blood pressure is influenced by height of pressure and age of subject; it is greater in emotional than in placid subjects; the greatest variations are met in phæochromocytoma, where it is usual to note some blanching of the face at the times of greatest blood pressure rise. The radial pulse may indicate an abnormality of rhythm requiring treatment or affecting prognosis; it may also show the presence of atheroma, but in my experience it is rare to be able to detect thickening of the radial artery before there is unmistakable evidence of cardiac or cerebral atheroma or both. Finally, the femoral pulses should always be felt because they provide the best simple guide to the presence of *coarctation of the aorta*. In coarctation, the femoral pulses are small and occasionally absent, and the summit of the pulse is delayed in comparison with the radial; careful examination of the back discloses enlarged tortuous collateral arteries; radiological examination of the thorax reveals scalloping of the lower margins of the ribs, and the absence of the full aortic arch. One or other of the peripheral pulses may also be lost in atheroma, polyarteritis nodosa or dissecting aneurysm of the aorta; the pulses of the lower limb are particularly so affected.

In the *nervous system* the most important examination is that of the fundus oculi because of the information it yields concerning prognosis. Abnormalities of the retinal arteries indicate the extent to which hypertension is associated with disease of small arteries and arterioles. Small glistening exudates and no papilloedema in a subject of over 50 years suggest arteriosclerotic retinopathy and the *benign phase* of hypertension. Large, ill-defined exudates in a younger subject with severe hypertension suggest the onset of the *malignant phase* and that no time should be lost before reducing blood pressure; the diagnosis of the malignant phase is, of course, completed by the presence of bilateral papilloedema. Severe headache, vomiting and papilloedema are also produced by cerebral tumour, and when coma, fits or focal

cerebral signs are added, cerebral tumour may be suspected. The co-existence of hypertension and cerebral tumour is rather uncommon, of malignant hypertension and cerebral tumour extremely rare.

delay. Should the arterial pressure be controlled adequately and papilloedema and focal cerebral signs nevertheless advance, a cerebral tumour should be considered. On the other hand, if a patient has only a mild or moderate hypertension and signs of a developing space occupying intracranial lesion, he should be investigated by cerebral angiography, encephalography and other appropriate measures, and, if necessary, explored with a view to diagnosis and treatment. Signs of a focal cerebral lesion attributable to hypertensive vascular disease are almost restricted to those who give a history of a "stroke" or little stroke, except for those in whom the intellect has been seriously impaired by widespread cerebral arteriosclerosis. Lesions of the individual peripheral nerves suggest polyarteritis nodosa.

In the respiratory system signs are usually secondary to heart disease, except when due to polyarteritis nodosa (Chapter 19). Hæmoptysis is a rare but definite manifestation of hypertension. Epistaxis is more common.

In the abdomen, bilateral renal tumours suggest *polycystic kidneys*. The rounded cysts may sometimes be felt; in addition, there is often a family history, and a history of attacks of pain, hæmaturia or renal infection; intravenous or retrograde pyelography show the characteristic elongations of the calyces. A unilateral renal tumour may signify a unilateral polycystic kidney, hydronephrosis or other lesion to be fully investigated by radiological and other methods. A pheochromocytoma, or the kidney displaced downwards by it, is occasionally felt.

The skin rarely shows abnormalities in hypertension apart from the redness and hirsuties of Cushing's disease, the curious contrast between slightly dilated vessels and the blanched skin between them that is sometimes seen in the cheeks in the malignant phase, and the purpura,¹ urea crust and desiccated skin of uræmia. Nodules and ulcers may suggest polyarteritis nodosa.

¹ A great deal of
malignant
hypertension

The urine should always be examined with especial care in any case with high blood pressure. A high specific gravity (1.024) or over, not due to glucose or protein, suggests intact renal function. A specific gravity fixed at 1.010 suggests advanced renal failure. A more deliberate test is the Volhard test of starving the patient of fluids from mid-day and measuring the specific gravity of the early morning urine ; this should rise to 1.024 or even as high as 1.030. The dilution test after drinking one and a half litres of water is frequently performed but I have not found it generally helpful.

The most important tests are those for protein and the microscopic examination. Protein, in general, means renal involvement, either primary renal disease or secondary to cardiac failure or to malignant hypertension ; the Bence-Jones proteinuria of multiple myeloma and the proteinuria of diabetes are other special cases. Microscopy, as Addis and Oliver (1931) pointed out, is of the greatest importance in deciding the nature of the renal lesion, because some of the components of the histological lesion may reach the urine. Microscopy should always be done on the centrifuged deposit of a *fresh* specimen of the urine by the clinician himself. The formed elements quickly disintegrate and reports on stale specimens from routine laboratories are always erroneous and may lead to serious errors in diagnosis. In this technological age, when the rôle of the clinician seems to be degenerating into a sorting-house for the paper slips which are delivered to him at his request from an assortment of special departments, nothing is to be more deplored than his failure, personally, to examine the urine. Examination of the urine may clinch the diagnosis of nephritis and pyelonephritis. *Type 1 nephritis* usually begins acutely with hæmaturia, slight œdema, mild hypertension and scanty urine ; the urine contains protein, abundant red cells and, in the early stages, red cell casts. In the chronic phase, hypertension is more severe, œdema is absent unless heart failure has occurred, renal function is impaired to any degree from slight to severe, the urine contains protein, a slight but definite excess of red cells, leucocytes and granular casts. *Type 2 nephritis* begins insidiously with œdema ; proteinuria is massive and hypertension absent. Later, œdema and proteinuria lessen, the blood pressure rises and renal function declines ; the urine contains protein, usually a slight excess of red and white cells and granular casts. *Chronic pyelonephritis* often has a history of vague pyrexial illness, frequency and renal pain ; renal function may or may not be impaired ; the urine contains a small amount of protein, a gross excess of white cells and very few casts ; culture of a catheter specimen reveals intermittent evidence of bacterial infection, usually by *E. coli*. Intravenous or retrograde pyelography may reveal distortion of the renal pelvis and calyces. The supervention of the malignant phase of hypertension is

accompanied by the presence of protein, red cells and casts in the urine ; in fact, in the presence of hypertensive neuro-retinopathy, the distinction between the malignant phases of essential hypertension, nephritis and pyelonephritis cannot always be made from the urine or renal function (unless these are normal, as they may be in the early stages of malignant essential hypertension), but is made largely on the history.

A more accurate estimate of the rate of excretion of formed elements in the urine may be obtained by the method of Addis. The patient is deprived of fluids for twenty-four hours, during the last twelve of which urine is collected. The volume of the twelve-hour collection is measured, 10 ml. is centrifuged, and the top 9.5 ml. pipetted off. The remaining 0.5 ml. is mixed and the formed elements counted in a blood counting chamber.

The Place of Laboratory and other Tests

Routine Tests

The Blood. A high erythrocyte sedimentation rate is common in uræmia and, in the absence of uræmia, usual only in polyarteritis nodosa and the acute phases of nephritis and pyelonephritis. Leucocytosis occurs in the acute phases of pyelonephritis and polyarteritis nodosa. Anæmia is usual in the presence of renal failure and is common in chronic pyelonephritis ; in the absence of these diseases, rapidly developing anæmia, not due to blood loss, suggests polyarteritis nodosa.

Electrocardiogram. An electrocardiogram should be taken in all patients over the age of 40, and in others where indicated, because of the information it may yield on abnormalities of rhythm, conduction and technique.

tior
Arr

properly. renal pulses is not doing his job

Tests of renal function should be performed in all cases because of the importance of kidney involvement to diagnosis and prognosis. The concentration test has been mentioned already. A test with similar object is the urea concentration test of MacLean and de Wesselow. No fluid is given after 6 p.m., the bladder is emptied at,

say, 7 a.m., 15 g. urea in 100 ml. water is ingested and specimens collected at 8, 9 and 10 a.m. The urea concentration in one specimen at least should exceed 2.5 per cent. Should a diuresis occur and the urinary volumes of any specimen exceed 100 ml., the test must be repeated. The urea clearance test is very generally used, but its precision is not great because of its dependence on accurate timing of urine collections and the wide range of normal figures. Blood urea is not usually raised in the early stages of renal insufficiency; but it may be raised by extrarenal causes, such as dehydration and large ingestion of protein. All these tests of renal function are coarse tests, and some latitude is allowed in their interpretation. Renal clearances of inulin and thiosulphate on the one hand, and of diodone and para-amino-hippurate on the other, are used to measure glomerular filtration rate and effective renal blood flow. These estimations give much more precise information, but they require a skilled team and are beyond the scope of all but specially equipped laboratories.

Radiological Examination of the Urinary Tract

A plain X-ray of the kidneys should be taken in every case of hypertension since this will show the presence of stones, and gross abnormalities of size or position of the kidneys. In all cases of hypertension that are severe enough to need treatment an intravenous pyelogram should be done. When only one kidney is visualized, the test should be repeated, as this sometimes happens when both kidneys are normal. If one kidney shows an abnormality while the other kidney appears normal, cystoscopy should be performed and both ureters catheterized. Timed collections of urine should be made after the ingestion of 15 g. urea or the injection of indigo carmine, so that an estimate of differential renal function can be made. Retrograde pyelography should then be performed. If one kidney is normal to such tests and the other abnormal, then, in a moderate or severe hypertension, there is a strong case for excising the abnormal kidney with the hope of materially reducing the arterial pressure (Chapters 17 and 18). If both kidneys are equally abnormal, nephrectomy is contra-indicated. If one kidney is much more grossly affected than the other, but both are clearly abnormal, then again, in my experience, excising the more affected kidney is not indicated, since the hypertension is not usually improved, and the renal reserve is materially reduced.

Aortography. When all other efforts to demonstrate the cause of severe hypertension in a young person have failed, aortography should be considered, particularly if there is a history suggestive of renal pain or if radiological examination suggests a recent decrease in size of one kidney (see Chapter 18).

Blood Pressure Tests

The "sedation" and "cold pressor" tests, and 24-hour records of blood pressure were introduced to assess the contribution made by over-action of the sympathetic nerves, and to forecast the effects of sympathectomy. In the event, they have proved to do neither, and the first and second are now obsolete. Since arterial pressure is a variable quantity, the more numerous the observations the more accurately is its range defined. Repeated measurements are desirable before treatment is instituted, and essential to control therapy. Before instituting therapy, I prefer to have several measurements each day for a week rather than having hourly measurements for 24 hours. The physician should always beware lest his patients' spirits rise and fall inversely as the mercury in the manometer.

Urinary Excretion of Pressor Amines

The rate of excretion in the urine of adrenaline and noradrenaline should be estimated in all patients having attacks that resemble those of phaeochromocytoma, and in any other patients in whom there is a strong suspicion that such a tumour may exist.

MANAGEMENT

Matters requiring urgent Attention

The doctor may be called to see his patient with hypertension urgently because of the sudden development of a complication. Such are hypertensive fits, a cerebral vascular accident, left ventricular failure, ruptured aorta, and myocardial infarction, the treatment of which has been described in Chapter 15. Cardiac failure also requires urgent treatment (p. 335). So may suppression of urine in those diseases in which it occurs (p. 342). The other condition requiring urgent treatment is the malignant phase. No time should be lost before controlling arterial pressure, as described in Chapter 15, even though the underlying cause of the high blood pressure may not have been established. Once the blood pressure is controlled, the full investigation of the patient may be undertaken at leisure, with the assurance that should a removable cause be found, the least possible damage to the vascular system will have occurred before the causal lesion is dealt with.

Removal or Treatment of a Cause of Hypertension

There is nothing so rewarding as to be able to remove a cause of hypertension. Removable causes include chromaffin tumours (Chapter 20), coarctation of the aorta (Chapter 22), certain kinds of kidney

say, 7 a.m., 15 g. urea in 100 ml. water is ingested and specimens collected at 8, 9 and 10 a.m. The urea concentration in one specimen at least should exceed 2.5 per cent. Should a diuresis occur and the urinary volumes of any specimen exceed 100 ml., the test must be repeated. The urea clearance test is very generally used, but its precision is not great because of its dependence on accurate timing of urine collections and the wide range of normal figures. Blood urea is not usually raised in the early stages of renal insufficiency; but it may be raised by extrarenal causes, such as dehydration and large ingestion of protein. All these tests of renal function are coarse tests, and some latitude is allowed in their interpretation. Renal clearances of inulin and thiosulphate on the one hand, and of diodone and para-amino-hippurate on the other, are used to measure glomerular filtration rate and effective renal blood flow. These estimations give much more precise information, but they require a skilled team and are beyond the scope of all but specially equipped laboratories.

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Aortography. When all other efforts to demonstrate the cause of severe hypertension in a young person have failed, aortography should be considered, particularly if there is a history suggestive of renal pain or if radiological examination suggests a recent decrease in size of one kidney (see Chapter 18).

outlook appears dark indeed, will help to preserve morale. Nor should the contribution of anxiety and mental conflict to hypertension be overlooked. Again, the doctor by listening to the patients' story and by his wise counsel may succeed in removing both disturbances. This aspect of management is, of course, not peculiar to hypertension ; it is an essential part of good doctoring whatever the patients' illness.

lesion that are unilateral (Chapters 17 and 18), and Cushing's syndrome treated by excision of an adrenal tumour or subtotal adrenalectomy (Chapter 21). The possibility that prostatic obstruction may contribute to the hypertension should not be overlooked, and this lesion, if present, should be dealt with surgically. Polyarteritis nodosa may be controlled, at least partly, by cortisone; nevertheless, hypertension may develop as the kidney lesions heal. Pyelonephritis should be adequately treated by antibiotics and the surgical correction of an anatomical lesion of the urinary tract, should this be a feasible proposition. The treatment of nephritis is not very satisfactory and the fuller discussion in Chapter 16 should be consulted. Even if the apparent cause is removed, hypertension may persist; and in many of the above conditions, treatment, even if successful in arresting the course of the causal lesion, may leave the hypertension unaltered.

Treatment of the Hypertension

The indications for treatment of the hypertension itself are much the same whether the hypertension is primary or essential, or secondary to some other lesion, provided, of course, that the other lesion cannot be removed, or that the hypertension persists after its removal. The indications are given on p. 316 and a summary of the treatment of hypertension is given on pp. 336, *et seq.* In those cases where reduction of blood pressure is required, the hypotensive drugs offer the treatment of choice, but make demands on the patient that can only be fulfilled by an intelligent patient of good morale; sympathectomy and total adrenalectomy would seem to offer the second and third lines of defence, but in my view the latter is rather in the nature of a forlorn hope. Salt-free diet may be considered; but it makes even greater demands on the patient than do the hypotensive drugs and requires the same qualities of intelligence and morale.

General Management of the Patient

In cases where the cause of hypertension cannot be removed, the patient is condemned to live with his disability for many years, at least if his doctors achieve their objective of keeping him alive. It is extremely important that no unnecessary restrictions should be placed on the patient's conduct, and that so far as possible he should make his contribution to the community in which he lives, and thus retain his own self-respect. The doctor can always do much by wise counsel, both as to the general conduct of life, and as to how particular emergencies should be met. In the ups and downs of the patients' disease, the doctor's helpful and encouraging attitude, when to the patient the

7. These tables are only strictly applicable to blood pressures estimated under conditions similar to those in our population sample (p. 159). Even, however, under the rather more diverse conditions surrounding the measurement of pressure of our relatives, the use of these scores was illuminating.

APPENDIX I

CALCULATION OF AGE AND SEX-ADJUSTED SCORE

(Hamilton, Pickering, Roberts and Sowry, *Clin. Sci.*, 1954, 13, 37)

Procedure

1. Find the expected pressure for the appropriate age and sex in the top horizontal columns of Tables A, B, C and D.

2. Calculate the deviation (x) of the observed from the expected pressure. If the observed pressure exceeds the expected, the deviation has a plus sign, if it is less, a minus sign.

3. Correct the observed deviation (x) for the effects of variance by the lower half of Tables A, B, C and D. The left-hand column gives the observed deviation (x); the figures in the same horizontal column give the corrected deviation for the age of the patient. The figure so selected is the final age-adjusted score and carries a plus or minus sign as previously described.

4. Over most of the range of possible pressures the age and sex-adjusted score can be read off directly. For example, the first part of Section A shows that a woman of 40 with a systolic pressure of 170 mm. is 40 mm. above expectation. The second part of Section A shows that a deviation of ± 40 at age 40 corresponds to ± 55 as at age 60. The score is therefore + 55.

5. Where the values along a horizontal line in the second part of a section are changing by more than 5 mm. from one five-year age group to the next, interpolation should be used. For example, a woman of 24 has a systolic pressure of 170 mm., 50 mm. above expectation. This deviation for the age group 20-24 corresponds to + 125 as at age 60. For the age group 25-29 the corresponding score is + 105. These scores apply to the mid-points of the age groups, viz. 22 years and 27 years. The rate of change over the five-year interval is 4 mm. per year, hence the score is $125 - (2 \times 4) = + 115$.

6. For deviations from expectation outside the range of the table, multiply the deviation by the multiplier at the foot of the appropriate column. Note that interpolation as in 2 above will usually be necessary. For example, a woman of 24 has a systolic pressure of 200 mm., 80 mm. above expectation. $80 \times 2.453 = 195$, which applies to the age group mid-point of 22 years. The table shows that at 27 years the score would be + 170; hence the score for 24 years is + 185.

B. Women, Diastolic.

Age last birthday 10-23 24-34 35-43 44-53 54-64 65-84
 Expected pressure mm 70 85 80 85 90 95

Obs deviation from expectation mm. ±	Corresponding deviation as at 60th birthday														
	Age last birthday														
	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84
5	10	10	10	10	5	5	5	5	5	5	5	5	5	5	5
10	20	20	15	15	15	15	10	10	10	10	10	10	10	10	10
15	30	30	25	25	20	20	20	15	15	15	15	15	15	15	15
20	40	40	35	35	30	25	25	25	20	20	20	20	20	20	20
25	50	50	45	40	35	35	30	30	25	25	25	25	25	25	25
30	60	60	55	50	45	40	35	35	30	30	30	30	30	30	30
35	70	70	65	60	50	50	45	40	40	35	35	35	35	35	35
40	80	80	75	75	65	55	50	45	45	40	40	40	40	40	40
45	90	90	80	75	65	60	55	50	50	45	45	45	45	45	45
50	100	100	90	85	75	70	60	60	55	50	50	50	50	50	50
55	110	110	100	90	80	75	70	65	60	55	55	55	55	55	55
60	125	120	110	100	90	80	75	70	65	60	60	60	60	60	60
65					95	95	85	80	75	70	70	65	65	65	65
70					100	100	95	85	80	75	76	70	70	70	70
75						110	100	95	85	80	80	75	75	70	70
80							105	100	90	85	85	80	80	75	75
85															
Multiplier	2.044	1.068	1.820	1.633	1.406	1.362	1.249	1.158	1.084	1.023	0.978	0.943	0.917	0.901	0.884

D. Men, Diastolic.

Obs. deviation from expectation mm. ±	Corresponding deviation as at birth birthday															Multiplier
	Age last birthday															
	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	
5	5	5	10	10	10	5	5	5	5	5	5	5	5	5	5	
10	15	15	15	15	15	15	10	10	10	10	10	10	10	10	10	
15	20	20	25	25	25	25	20	15	15	15	15	15	15	15	15	
20	25	30	30	35	30	30	25	20	20	20	20	20	20	20	20	
25	35	35	40	40	40	35	30	25	25	25	25	25	25	25	25	
30	40	45	50	50	50	45	35	30	30	30	30	30	30	30	30	
35	45	50	55	60	65	50	45	40	35	35	35	35	35	35	35	
40	50	60	65	70	75	65	55	50	45	45	45	45	45	45	45	
45	55	70	75	80	85	75	65	60	55	55	55	55	55	55	55	
50	60	80	90	100	105	90	80	75	70	65	65	65	65	65	65	
55	70	90	100	110	115	100	90	85	80	75	75	75	75	75	75	
60	80	100	110	120	125	110	100	95	90	85	85	85	85	85	85	
65	85	105	115	125	130	115	105	100	95	90	90	90	90	90	90	
70	90	110	120	130	135	120	110	100	95	90	90	90	90	90	90	
75	95	120	130	140	145	125	115	105	100	95	95	95	95	95	95	
80	100	125	135	145	150	130	120	110	105	100	100	100	100	100	100	
85	105	130	140	150	155	135	125	115	110	105	105	105	105	105	105	
90	110	135	145	155	160	140	130	120	115	110	110	110	110	110	110	
95	115	140	150	160	165	145	135	125	120	115	115	115	115	115	115	
100	120	145	155	165	170	150	140	130	125	120	120	120	120	120	120	
105	125	150	160	170	175	155	145	135	130	125	125	125	125	125	125	
110	130	155	165	175	180	160	150	140	135	130	130	130	130	130	130	
115	135	160	170	180	185	165	155	145	140	135	135	135	135	135	135	
120	140	165	175	185	190	170	160	150	145	140	140	140	140	140	140	
125	145	170	180	190	195	175	165	155	150	145	145	145	145	145	145	
130	150	175	185	195	200	180	170	160	155	150	150	150	150	150	150	
135	155	180	190	200	205	185	175	165	160	155	155	155	155	155	155	
140	160	185	195	205	210	190	180	170	165	160	160	160	160	160	160	
145	165	190	200	210	215	195	185	175	170	165	165	165	165	165	165	
150	170	195	205	215	220	200	190	180	175	170	170	170	170	170	170	
155	175	200	210	220	225	205	195	185	180	175	175	175	175	175	175	
160	180	205	215	225	230	210	200	190	185	180	180	180	180	180	180	
165	185	210	220	230	235	215	205	195	190	185	185	185	185	185	185	
170	190	215	225	235	240	220	210	200	195	190	190	190	190	190	190	
175	195	220	230	240	245	225	215	205	200	195	195	195	195	195	195	
180	200	225	235	245	250	230	220	210	205	200	200	200	200	200	200	
185	205	230	240	250	255	235	225	215	210	205	205	205	205	205	205	
190	210	235	245	255	260	240	230	220	215	210	210	210	210	210	210	
195	215	240	250	260	265	245	235	225	220	215	215	215	215	215	215	
200	220	245	255	265	270	250	240	230	225	220	220	220	220	220	220	
205	225	250	260	270	275	255	245	235	230	225	225	225	225	225	225	
210	230	255	265	275	280	260	250	240	235	230	230	230	230	230	230	
215	235	260	270	280	285	265	255	245	240	235	235	235	235	235	235	
220	240	265	275	285	290	270	260	250	245	240	240	240	240	240	240	
225	245	270	280	290	295	275	265	255	250	245	245	245	245	245	245	
230	250	275	285	295	300	280	270	260	255	250	250	250	250	250	250	
235	255	280	290	300	305	285	275	265	260	255	255	255	255	255	255	
240	260	285	295	305	310	290	280	270	265	260	260	260	260	260	260	
245	265	290	300	310	315	295	285	275	270	265	265	265	265	265	265	
250	270	295	305	315	320	300	290	280	275	270	270	270	270	270	270	
255	275	300	310	320	325	305	295	285	280	275	275	275	275	275	275	
260	280	305	315	325	330	310	300	290	285	280	280	280	280	280	280	
265	285	310	320	330	335	315	305	295	290	285	285	285	285	285	285	
270	290	315	325	335	340	320	310	300	295	290	290	290	290	290	290	
275	295	320	330	340	345	325	315	305	300	295	295	295	295	295	295	
280	300	325	335	345	350	330	320	310	305	300	300	300	300	300	300	
285	305	330	340	350	355	335	325	315	310	305	305	305	305	305	305	
290	310	335	345	355	360	340	330	320	315	310	310	310	310	310	310	
295	315	340	350	360	365	345	335	325	320	315	315	315	315	315	315	
300	320	345	355	365	370	350	340	330	325	320	320	320	320	320	320	
305	325	350	360	370	375	355	345	335	330	325	325	325	325	325	325	
310	330	355	365	375	380	360	350	340	335	330	330	330	330	330	330	
315	335	360	370	380	385	365	355	345	340	335	335	335	335	335	335	
320	340	365	375	385	390	370	360	350	345	340	340	340	340	340	340	
325	345	370	380	390	395	375	365	355	350	345	345	345	345	345	345	
330	350	375	385	395	400	380	370	360	355	350	350	350	350	350	350	
335	355	380	390	400	405	385	375	365	360	355	355	355	355	355	355	
340	360	385	395	405	410	390	380	370	365	360	360	360	360	360	360	
345	365	390	400	410	415	395	385	375	370	365	365	365	365	365	365	
350	370	395	405	415	420	400	390	380	375	370	370	370	370	370	370	
355	375	400	410	420	425	405	395	385	380	375	375	375	375	375	375	
360	380	405	415	425	430	410	400	390	385	380	380	380	380	380	380	
365	385	410	420	430	435	415	405	395	390	385	385	385	385	385	385	
370	390	415	425	435	440	420	410	400	395	390	390	390	390	390	390	
375	395	420	430	440	445	425	415	405	400	395	395	395	395	395	395	
380	400	425	435	445	450	430	420	410	405	400	400	400	400	400	400	
385	405	430	440	450	455	435	425	415	410	405	405	405	405	405	405	
390	410	435	445	455	460	440	430	420	415	410	410	410	410	410	410	
395	415	440	450	460	465	445	435	425	420	415	415	415	415	415	415	
400	420	445	455	465	470	450	440	430	425	420	420	420	420	420	420	
405	425	450	460	470	475	455	445	435	430	425	425	425	425	425	425	
410	430	455	465	475	480	460	450	440	435	430	430	430	430	430	430	
415	435	460	470	480	485	465	455	445	440	435	435	435	435	435	435	
420	440	465	475	485	490	470	460	450	445	440	440	440	440	440	440	
425	445	470	480	490	495	475	465	455	450	445	445	445	445	445	445	
430	450	475	485	495	500	480	470	460	455	450	450	450	450	450	450	
435	455	480	490	500	505	485	475	465	460	455	455	455	455	455	455	
440	460	485	495	505	510	490	480	470	465	460	460	460	460	460	460	
445	465	490	500	510	515	495	485	475	470	465	465	465	465	465	465	
450	470	495	505	515	520	500	490	480	475	470	470	470	470	470	470	
455	475	500	510	520	525	505	495	485	480	475	475	475	475	475	475	
460	480	505	515	525	530	510	500	490	485	480	480	480	480	480	480	
465	485	510	520	530	535	515	505	495	490	485	485	485	485	485	485	
470	490	515	525	535	540	520	510	500	495	490	490	490	490			

C. Men, Systolic.

Age last birthday 10-15 16-20 31-39 40-44 45-52 53-57 58-61 62-65 66-69 70-73 74-76 77-79 80-82 83-84
 Expected pressure mm. 115 120 125 130 135 140 145 150 155 160 165 170 175 180

Corresponding deviation as at birth birthday
 Age last birthday

Obs. deviation from expectation mm. \pm	Corresponding deviation as at birth birthday Age last birthday														Multiplier
	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84
5	10	10	10	10	10	10	10	5	5	5	5	5	5	5	5
10	15	20	25	25	20	20	15	15	10	10	10	10	10	10	10
15	25	30	35	35	30	30	25	25	20	15	15	15	15	15	10
20	35	40	45	50	45	40	30	30	25	20	20	20	20	15	15
25	40	50	60	60	55	45	40	35	30	30	25	25	20	20	20
30	50	60	70	75	65	55	50	40	35	35	30	30	25	25	25
35	60	70	85	85	75	65	65	50	45	40	35	35	30	30	30
40	65	80	95	95	90	75	65	55	50	45	40	40	35	35	30
45	75	90	105	110	100	85	75	65	60	55	45	40	40	40	35
50	85	105	120	120	110	95	80	70	60	55	50	45	45	40	40
55	90	115	130	135	120	105	90	75	70	60	55	50	50	45	45
60	100	125	140	145	130	115	95	85	75	65	60	55	55	50	50
65	110	135	155	160	145	125	105	90	80	70	65	60	55	55	55
70		145	165	170	155	130	115	100	85	80	70	65	60	60	55
75			180	180	165	140	120	105	90	85	75	70	65	65	60
80				195	175	150	130	110	100	90	80	75	70	65	65
85				205	185	160	135	120	105	95	85	80	75	70	70
90				220	200	170	145	125	110	100	90	85	80	75	75
95					210	180	155	135	115	105	95	90	85	80	75
100					220	190	160	140	125	110	100	95	90	85	80
105					230	200	170	145	120	115	105	100	95	90	80
110						210	175	155	135	120	110	105	100		
115						215	185	160	140	125	115	105			
120						225	195	165	150	135					
125						235	200	175	155	140					
	1-680	2 952	2-369	2-424	2 200	1-869	1 612	1-395	1-231	1-107	1-012	0 940	0-884	0 842	0 812

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